Effects of exercise on sleep and nocturnal arousal in patients with unipolar depression

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List of Abbreviations

ICD	International Classification of Diseases
DSM	Diagnostic & Statistical Manual of Mental Disorders
ICSD	International Classification of Sleep Disorders
CBT-I	cognitive behavioral therapy for insomnia
EEG	electroencephalography, electroencephalographic
HRV	heart rate variability
RMSSD	root mean square of successive differences of normal-to-normal intervals
REM	rapid eye movement
Bmal1	brain and muscle ARNT-Like 1
PGC1-α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
IL-6	interleukin-6
IL-1ra	interleukin-1 receptor antagonist
BDNF	brain-derived neurotrophic factor
DBHB	d-beta-hydroxybutyrate
HDAC2/3	histone deacetylases 2 and 3
IGF-1	insulin-like growth factor-1
FNDC5	fibronectin type III domain-containing protein 5
CTSB	cathepsin B
OC	osteocalcin
SWA	slow-wave activity
FGF21	fibroblast growth factor 21
PPARα	peroxisome proliferator-activated receptor alpha
KYN	kynurenine
KYNA	kynurenic acid
KAT	kynurenine aminotransferase

Summary

Background

Unipolar depression is a debilitating disease and one of the leading causes of global disease burden. Unipolar depression is bidirectionally associated with insomnia and attenuated heart rate variability. Insomnia has a negative effect on disease trajectory across all treatment phases in depression. Attenuated heart rate variability is one of the pathophysiological mechanisms explaining the increased risk of cardiovascular disease in patients with depression. Approximately one-third of the patients do not remit when treated with guideline therapies for depression, i.e., psychotherapy and pharmacotherapy. Moreover, insomnia is one of the most frequent residual symptoms in those who respond or remit. Lastly, guideline therapies do not seem to improve heart rate variability. Therefore, adjuvant therapies to improve depressive and insomnia symptoms and heart rate variability are need. Exercise is a promising auxiliary treatment based on previous research, but multiple knowledge gaps remain.

Aims

This Ph.D. project aimed to address important knowledge gaps. The first aim was to summarize the existing research concerning the effects of aerobic, resistance, and mind-body exercise on sleep quality in patients with unipolar depression. The second aim was to quantify the effect of a single bout of moderate-intensity aerobic exercise performed in the afternoon on sleep outcomes in patients with unipolar depression. The third aim was to quantify the effect of a single bout of moderate-intensity aerobic exercise performed in the afternoon on mood and adverse effects. The fourth and last aim was to quantify the effect of a single bout of moderate-intensity aerobic exercise performed in the afternoon on nocturnal and pre-sleep arousal.

Methods

A systematic review with network meta-analysis and a randomized controlled trial were conducted within this Ph.D. project. The systematic review (PROSPERO CRD42019115705) was conducted according to the PRISMA network meta-analysis extension and AMSTAR2 guidelines. A systematic search was conducted in multiple electronic bibliographic databases (PubMed, EMBASE, Cochrane Library, PsycINFO, Sportdiscus, CINHAL, OpenGrey, ProQuest Dissertations & Theses A&I, Clinicaltrials.gov, and WHO International Clinical Trials Registry) from their inception until February 12th, 2020. Randomized controlled trials investigating the effects of regular aerobic, resistance, or mind-body exercise on self- or observer-reported sleep quality in patients with depression were included. Network meta-analysis was conducted, and the network geometry, forest plots, and league tables were reported.

The trial (NCT03673397) was a two-arm parallel-group, randomized, outcome assessor-blinded, controlled, superiority trial. It was conducted and reported in compliance with SPIRIT, GRAPH, FAIR, CONSORT, GCP, and GDPR guidelines and directives. The trial took place in the OBERWAID clinic. Patients between 18 and 65 years of age with a primary diagnosis of unipolar depression were included. The intervention was a single 30-minute bout of moderate aerobic exercise. The control group sat and read for 30 minutes. The primary outcome was sleep efficiency measured by polysomnography. Secondary outcomes were other polysomnographic variables, subjective sleep quality, daytime sleepiness, mood states, adverse events, pre-sleep arousal, as well as pre-sleep and nocturnal heart rate variability.

Results

Publication 1: The effects of aerobic, resistance, and meditative movement exercise on sleep in individuals with depression: protocol for a systematic review and network meta-analysis [1]
This publication provides a thorough account of the purpose and methodology of the systematic revie and network meta-analysis. The report adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guideline.

Publication 2: The effects of exercise on sleep in unipolar depression: a systematic review and network meta-analysis [2]
The network meta-analysis was based on 17 trials with N = 1645 patients randomized to 13 treatments yielding 35 comparisons. The confidence in the mixed (i.e., direct and indirect) evidence was moderate (43% of comparisons), low (39% of comparisons), or very low (18% of comparisons). All exercise types and intensity levels except moderate aerobic exercise improved sleep quality more than passive control. The effects of active control, mind-body exercise, treatment as usual, and vigorous aerobic exercise were similar. Vigorous strength exercise yielded a significantly larger effect on sleep quality than aerobic or mind-body exercise compared to passive control. None of the exercise modes or intensities was significantly less efficacious than treatment as usual. Adding moderate or vigorous aerobic exercise to treatment as usual resulted in slightly larger effect sizes, but these differences were not statistically significant. However, vigorous strength exercise alone or adding mind-body exercise to treatment as usual resulted in significantly larger effects than treatment as usual alone.

Publication 3: The acute effects of aerobic exercise on sleep in patients with depression: study protocol for a randomized controlled trial [3]
This publication presents the rationale, hypothesis, and procedures of the randomized controlled trial in detail. The publication was written in accordance with the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) statement.

Publication 4: The acute effects of aerobic exercise on sleep in patients with unipolar depression: a randomized controlled trial [4]
There was no evidence for an effect of allocation on polysomnographic sleep efficiency. This finding was confirmed in all sensitivity analyses (i.e., complete case and per-protocol analysis as well as excluding an influential data point). There was also no evidence that chronotype, expectancy, or

credibility altered the effect of allocation. No evidence of a correlation between exercise intensity (i.e., rate of perceived exertion and percent of maximal age-predicted heart rate) and sleep efficiency at follow-up was found. Furthermore, there was no evidence for an effect of allocation on any of the secondary objective or subjective measures of sleep or daytime sleepiness. However, there was a strong effect of allocation on mood immediately post-exercise. This effect was consistent across all subscales, with the intervention group showing decreases in negative and increases in positive mood states. Although there was a trend toward lower symptom severity in the intervention group compared to the control group immediately post-exercise, this effect was non-significant.

Publication 5: *The acute effects of aerobic exercise on nocturnal and pre-sleep arousal in patients with unipolar depression: a randomized controlled trial* [5]

There was no evidence for an effect of allocation on root mean square of successive differences of normal-to-normal intervals during the sleep period. All sensitivity analyses confirmed this finding (i.e., only using complete data, excluding patients who smoked, used either beta-blockers, any antidepressant, or only tricyclic antidepressants). Furthermore, no evidence suggested that allocation altered root mean square of successive differences of normal-to-normal intervals in any sleep stage (although N1 was not analyzed due to insufficient data). There was also no evidence to suggest that any of the other heart rate variability parameters were affected by allocation during the sleep period. Lastly, no evidence indicated that pre-sleep root mean square of successive differences of normal-to-normal intervals or pre-sleep somatic and cognitive arousal were altered by allocation.

Conclusions

The findings of the network meta-analysis confirm the salubrious effects of regular aerobic, resistance, and mind-body exercise for patients with depression. None of the investigated exercise types or intensities lowered subjective sleep quality. Vigorous resistance and mind-body exercise in combination with treatment as usual elicited the most substantial effects. Therefore, these exercise modes might be recommended to target sleep quality in patients with depression specifically. However, the confidence in these findings is low, and thus more research is needed. The results of publications 4 and 5 confirm previous findings, which found no evidence of an adverse effect of acute exercise after 02:00 pm on sleep-related outcomes. The absence of evidence was consistent across all outcomes of sleep, pre-sleep arousal, and heart rate variability. Thus, these findings question the validity of the exercise timing recommendations in sleep hygiene guidelines. Moreover, a single bout of moderate-intensity exercise lasting 30 minutes can be recommended to improve the mood of patients with depression. In summary, regular aerobic, resistance, and mind-body exercise can be recommended as an adjuvant treatment to improve mood and insomnia symptoms in patients with depression.

Chapter 1

Introduction

1 Introduction

Sleep is a biologically necessary behavior. Although the evolutionary origins of sleep are still unknown [6], it is vital for metabolic, immune, cardiovascular, endocrine, neuronal, and mental health [7–11] as well as daytime functioning [12, 13]. Conversely, acute and chronic sleep deprivation and subjective poor sleep quality have deleterious effects on physical and mental health [14, 15].

More specifically, sleep plays a central role in the etiopathogenesis of unipolar depression [16], a leading cause of disability worldwide [17]. Interestingly, there is a complex interconnection between sleep, unipolar depression, and psychophysiological hyperarousal.

Exercise, on the other hand, is medicine [18]. The positive effects of exercise on depressive symptoms [19], sleep [20], and hyperarousal [21–23] in the general population are supported by a plethora of evidence. However, there are considerable knowledge gaps concerning exercise's effect on sleep and hyperarousal in patients with depression. This Ph.D. project aimed to close some of these gaps.

In this Ph.D. thesis, results of previous trials were meta-analytically aggregated to quantify the effects of aerobic, strength, and mind-body exercise on sleep in patients with depression (publication 1, protocol and publication 2, network meta-analysis). A randomized controlled trial was planned (publication 3) to address the gap in the literature concerning the acute effects of aerobic exercise on sleep and hyperarousal in patients with depression. Herein, the effects of a single bout of moderate-intensity aerobic exercise on sleep, mood, and adverse outcomes (publication 4), as well as nocturnal and pre-sleep arousal (publication 5), were investigated.

The topics of depression, insomnia, and hyperarousal, including current treatment recommendations, will be presented first in the following sections. Second, the interaction between depression, insomnia, and hyperarousal will be discussed. Third, the effects of exercise within the context of depression, insomnia, and hyperarousal are presented. Knowledge gaps and the need for additional treatments will also be highlighted throughout the introduction.

1.1 Depression

Unipolar depression, henceforth referred to as depression, is characterized by persistent depressed mood or anhedonia combined with other psychological, physical, and behavioral symptoms [24]. Several factors make depression one of the most relevant disorders worldwide. Lifetime prevalence is high, estimated to be between 10 and 15% [25]. Depression is a debilitating disease affecting most areas of life. It reduces quality-adjusted life-years [26] and quality-adjusted life expectancy [27]. Depression causes a significant socio-economic burden through the increased risk of absenteeism, presenteeism, disability, early retirement [23, 24], and higher health care costs [28]. It is important to note that treatment-resistant depression [29] and minor depression [30] cause a substantial economic burden. Depression is also associated with an increased mortality burden, primarily due to suicide and cardiovascular deaths [31, 32]. In summary, depression is projected to become the leading cause of disease burden worldwide by 2030 [33].

Guidelines specify psychotherapy, pharmacotherapy, or both as first-line treatments, depending on the symptom severity [34–36]. Meta-analysis shows that compared to placebo, psychotherapy and pharmacotherapy have small effect sizes (0.35 and 0.37, respectively), with combined therapy showing

a moderate to large effect size (0.74) [37]. One of the most extensive effectiveness trials (STAR*D trial with four treatment steps in over 4000 patients) showed that treatment with pharmacotherapy, cognitive behavioral therapy, or both led to remission in two-thirds of the patients [38]. A meta-analysis of psychotherapy for depression found similar results, with 62% of patients being in remission after the treatment [39]. Conversely, approximately one-third of the patients do not recover with first-line therapies. Moreover, most patients prefer non-pharmacological treatments for depression [40], and long-term non-adherence to antidepressants is estimated to be approximately 50% [41]. Hence, there is a need for further adjuvant non-pharmacological treatment options.

1.2 Insomnia

Insomnia – both a symptom and a diagnosis – encompasses problems initiating or maintaining sleep despite adequate opportunity for sleep resulting in daytime impairments [42]. Non-restorative or perception of poor sleep quality is frequently associated with insomnia. The majority of patients with insomnia have comorbidities [43].

The societal consequences of insomnia are substantial. Prevalence rates of insomnia symptoms and diagnosis in the general population are estimated at 10-40% and 5-10%, respectively, depending on the definition used [44–48]. Insomnia is associated with a reduced quality of life [49] and role impairment [50]. Insomnia is inversely associated with work productivity [51], and insufficient sleep results in annuals costs of 1%-3% of gross domestic product [52]. Insufficient sleep is also a risk factor for metabolic [53–55], cardiovascular [56–60], mental [11], and neurodegenerative [61–63] disorders. However, evidence whether insomnia is an independent risk factor for mortality is equivocal [64, 65].

Historically, diagnostic systems have subdivided insomnia based on etiological distinctions. The International Classification of Diseases (ICD) differentiates ‘organic’ and ‘nonorganic’ insomnia. The Diagnostic & Statistical Manual of Mental Disorders (DSM) and the International Classification of Sleep Disorders (ICSD) classified insomnia as ‘primary’ and ‘secondary.’ However, due to insufficient evidence for a mechanistic distinction between primary and secondary insomnia, this dichotomy has been challenged [66]. Consequently, the latest versions of diagnostic manuals (DSM-5, ICSD-3, and ICD-11) have combined primary and secondary insomnia. Thus, a paradigm shift towards recommending specific treatments for comorbid insomnia has occurred.

According to guidelines, Cognitive Behavioral Therapy for Insomnia (CBT-I) and pharmacotherapy are considered first- and second-line therapies for insomnia (regardless of whether comorbidities are present or not) [67, 68]. Although CBT-I is highly effective [69], the number of trained specialists limits the accessibility of this treatment [70, 71]. Multiple meta-analyses have confirmed that pharmacological agents (e.g., non-benzodiazepines, sedating antidepressants) have statistically small but clinically meaningful effects [72–75]. However, pharmacotherapy for insomnia has several limitations: 1) prescription frequency and 2) dosage frequently exceed recommendations of health agencies, in particular for patients with comorbid insomnia [76–78], 3) long-term use of hypnotics does not lead to remission [79, 80], 4) there are potentially severe adverse effects [81–84], and 5) patients often prefer non-pharmacological therapies [85–88]. Therefore, there is a need to develop further non-pharmacological treatments for insomnia.

1.3 Hyperarousal

Definitions of hyperarousal vary, but most definitions have the following factors in common: a state of increased activation and responsiveness which manifests itself across multiple psychophysiological biomarkers. Measures of arousal include questionnaires and objective measures such as electrodermal activity, hormone secretion, metabolic measures, electroencephalographic (EEG) activity, and heart rate variability (HRV) [89, 90]. HRV, a measure of autonomic cardiac modulation, is arguably one of the most commonly used measures of arousal.

HRV is defined as the "oscillation in the interval between consecutive heartbeats as well as the oscillations between consecutive instantaneous heart rates" [91]. HRV is typically measured over 24 hours or a period of five minutes, using time-domain, frequency-domain, or non-linear indices [92]. Despite a large number of HRV indices, the physiological meaning of these markers is often unclear. Only the root mean square of successive differences of normal-to-normal intervals (RMSSD) and high-frequency power (0.15-0.4 Hz [ms2]) are generally accepted indicators of vagal modulation [93, 94]. None of the currently available HRV markers exclusively denotes sympathetic modulation. Henceforth, lower HRV refers to a lower vagally-mediated HRV (e.g., lower RMSSD).

Though not a diagnosis in its own right, chronic hyperarousal is associated with or predictive for multiple disorders. HRV has been identified as an index of self-regulation [95]. Specifically, low resting high-frequency HRV and disproportionate high-frequency HRV reactivity to emotional challenge are transdiagnostic biomarkers of psychopathology [96]. HRV is associated with dementia [97], type two diabetes [98], metabolic syndrome [99], autoimmune diseases [100], and gastrointestinal disorders [101]. HRV-dysregulation is also a predictive factor for cardiovascular morbidity and mortality [102–106].

Since hyperarousal is not considered a diagnosis, there is no guideline treatment. Instead, hyperarousal is addressed in the context of the disorders or the comorbidities which are being treated. However, multiple interventions have been designed to reduce arousal specifically. These include biofeedback as an add-on to psychotherapy [107, 108], mindfulness meditation [109], and exercise [110, 111], amongst others.

1.4 The crossroads of depression, insomnia, and arousal

1.4.1 Depression and insomnia

Prospective studies have discovered a bidirectional prospective relationship between depression and insomnia [16, 112–119]. This finding is also supported by evidence from Mendelian randomization studies [120, 121]. More specifically, the sleep onset insomnia subtype might drive this bidirectional risk [122, 123]. Interestingly, sleep reactivity (i.e., the vulnerability to stress-related sleep disturbances) is associated with depression, and this association is partially mediated by insomnia [124]. Insomnia prevalence in patients with manifest depression is reported to be up to 90% [117, 125].

Insomnia symptoms strongly influence the acute treatment phase in depression. Insomnia is associated with an attenuated response to psychotherapy, pharmacotherapy, and a combination of both [126–131]. Insufficient sleep also increases the risk of developing treatment-resistant depression,

suicidality, and death by suicide [132–136]. Contrariwise, insomnia improvements during treatment for depression are associated with increased rates of response and remission [128, 137], see Figure 1.

Insomnia also has a negative effect during the continuation and maintenance treatment phases. Sleep complaints are among the most common symptoms after treatment response [138] and remission [139]. The rate of residual sleep symptoms does not seem to differ between psychotherapy and pharmacotherapy [140]. The evidence concerning the risk of relapse due to residual sleep symptoms is mixed. Some trials show that residual sleep symptoms are a risk factor for relapse [141–145], while others find no effect [137, 146]. However, difficulties sleeping seem to be a prodromal symptom of depression recurrence [147–149]. Insomnia is associated with a lower general quality of life in individuals with mental disorders [150]. Sleep problems also increase the risk of early or disability retirement due to depression [151, 152].

Given the importance of insomnia in depression highlighted above, there is a consensus that insomnia symptoms necessitate specific treatment in patients with depression [153]. CBT-I improves sleep in patients with depression [154]. There is also strong evidence that insomnia-specific interventions, i.e., CBT-I, pharmacotherapy, or a combination of both, have a strong positive effect on mood in patients with depression [155, 156]. This positive effect of CBT-I on mood is partially mediated by improvements in sleep [157–159]. Accordingly, insomnia-specific adjunct pharmacotherapy improves depression response and remission rates significantly [160]. Nevertheless, despite the combined treatment of depression and insomnia, many patients do not respond or remit. This finding highlights the need for further adjuvant therapies to improve insomnia outcomes in patients with depression.

1.4.2 Depression and arousal

Diagnosis and severity of depression are inversely associated with HRV during the day [161–165] and night [166–170]. The inverse association seems to be driven by subjective sleep quality [166, 171]. Furthermore, the association might also be mediated by the increased rapid eye movement (REM) sleep typically seen in patients with depression [161, 172]. Patients with depression also have a blunted HRV response to stress [173]. The use of antidepressants might further aggravate low HRV in patients with depression. There is unambiguous evidence that tricyclic antidepressants lower HRV [162, 174–178]. Evidence concerning the effect of other classes of antidepressants on HRV is equivocal, suggesting no effect or a reduction in HRV [162, 174–178]. Lastly, multiple trials have revealed that reduced HRV is an antecedent to depression [179–181], see Figure 1.

HRV is a relevant biomarker in the treatment of depression. The interaction between baseline-HRV and anxious depression subtype is predictive of post-treatment depression outcome [182]. However, HRV does not seem to improve after 6-12 weeks of standard in-patient therapy (i.e., including psychotherapy and pharmacotherapy), despite clinically relevant effects on depressive symptoms [183]. Given the association between depression and HRV and adverse health outcomes associated with lower HRV (see sections 1.3 and 1.5.4), there is a need for adjuvant therapies that improve this biomarker in patients with depression.

1.4.3 Insomnia and arousal

Hyperarousal is considered one of the (but not the only) central etiopathogenic mechanisms of insomnia. This supposition is reflected by the role hyperarousal plays in two of the most widely accepted models of insomnia, the hyperarousal model [89] and the cognitive model [184]. A more

recent integrative pathophysiological model described hyperarousal as an "overarching theme" in insomnia [185]. Lower HRV is also associated with sleep reactivity, an essential factor in the stress-diathesis model of insomnia [186–190]. Arousal is a central factor in the development of insomnia, and once sleep disturbances become chronic. Manifest insomnia is associated with an increased level of arousal (i.e., increased sympathetic and decreased parasympathetic activity) during the day and night [191], see Figure 1.

CBT-I has been shown to reduce pre-sleep arousal [192], although it remains unclear whether this reduction mediates the improvements in insomnia [193]. However, CBT-I does not seem to improve nocturnal HRV despite the strong effects of CBT-I on insomnia [194, 195]. Other interventions, including hypnotics, acupuncture, aromatherapy, and paced breathing, have inconclusive effects on HRV [191].

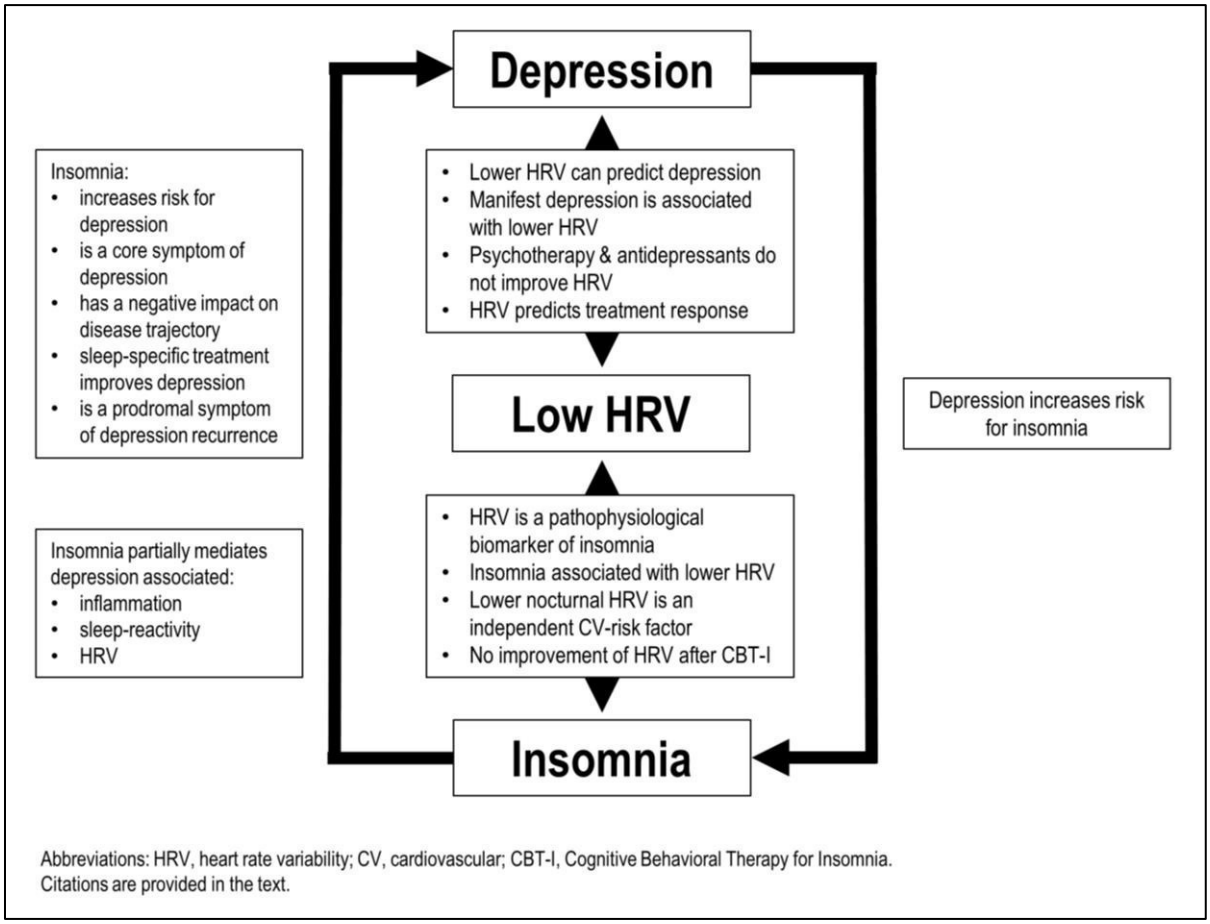

Figure 1: The interaction between depression, insomnia, and HRV.

1.5 Exercise for depression, insomnia, and arousal

Physical activity is defined as any skeletal muscle-induced bodily movement which results in energy expenditure above resting levels [196, 197]. Exercise is defined as planned, structured, and repetitive physical activity to improve or maintain components of physical fitness and health [196]. Aerobic exercise is defined as repeated movement patterns that involve large muscle groups, primarily use aerobic energy-producing systems, and are effective for improving cardiorespiratory endurance [198]. Resistance exercise is defined as muscles working against an applied force or weight, improving

skeletal muscle strength, power, endurance, or mass [198, 199]. Mind-body exercise is defined as slow movements or body positioning usually combined with specific breathing and relaxation techniques [200].

1.5.1 Exercise for depression

Exercise can be recommended in primary and secondary prevention of depression. Meta-analyses show that exercise has a protective effect against depression across the lifespan [201, 202]. Exercise also reduces depressive symptoms in people without clinical depression [19]. Robust evidence shows that regular aerobic exercise can improve cardiorespiratory fitness [203]. Higher cardiorespiratory fitness, in turn, reduces the risk of depressive symptoms and diagnosis of depression, as shown in prospective studies [204–207].

The European Psychiatric Association recommends exercise as an adjunctive treatment in depression [208]. The effects of aerobic, strength, and mind-body exercise on depressive symptoms are summarized below. Besides positive effects on depressive symptoms, exercise improves physical and psychological domains and overall quality of life with small to moderate effect sizes [209]. Moreover, exercise has lower dropout rates than usual treatment, placebo, and waitlist control [210].

Multiple meta-analyses have established that aerobic exercise improves symptoms of depression [207–211]. Meta-analyses have also shown that the effect of exercise on depressive symptoms does not significantly differ from psychotherapy or pharmacotherapy [211–213]. The volume and consistency of evidence for a positive effect of exercise on depression are most pronounced for supervised, moderate-to-vigorous intensity aerobic exercise, performed three times per week for at least eight weeks, and at least 30 minutes per session [214–217]. Exercise appears to be equally efficacious when performed in groups or individually [215, 216] and in out-patient or in-patient settings [218]. Combining exercise with behavioral [217] or antidepressant therapy [213] yielded larger effect sizes than behavioral or antidepressant therapy alone. Aerobic exercise improves symptoms of depression throughout the lifespan, including children and adolescents [219, 220] as well as older adults (>60 years) [221–223]. Regular aerobic exercise improves cardiorespiratory fitness in patients with depression [224], and this improvement might predict treatment response in adults with mild-to-moderate depression [225, 226]. Moreover, an increase in moderate-to-vigorous physical activity within the first four weeks of antidepressant treatment is associated with treatment response [227].

Resistance exercise has been less commonly investigated as a treatment for depression. Nevertheless, two meta-analyses including only clinically depressed patients revealed a large effect of resistance exercise on depressive symptoms [223, 228]. More specifically, increased resistance training intensity was associated with larger effect sizes [228]. Another meta-analysis on a heterogeneous population showed that resistance exercise improved depressive symptoms with a moderate effect size [229].

Mind-body exercises have a positive effect on depression. The meta-analysis of Zou et al. [230] established that Qi Gong improves response and remission rates compared to passive control in patients with clinical depression [230]. However, Qi Gong interventions are not superior when compared to active controls. A systematic review discovered that yoga had comparable effects to light-intensity aerobic exercise and antidepressants in clinically depressed patients [231]. However, the quality of evidence was low. A meta-analysis of mind-body exercises in older clinically depressed adults

(>65 years) concluded that exercise had a large positive effect on depressive symptoms [223]. Interestingly, mind-body exercise is also the only exercise modality which improves cognitive symptoms in depression [232, 233].

1.5.2 Exercise for insomnia in patients with depression

Multiple studies have assessed the effects of aerobic [144, 226, 234–238], resistance [239–241], and mind-body exercises [235, 236, 242–248] on sleep in patients with depression. These trials generally found a positive effect of all exercise modalities. However, a narrative synthesis of these trials is futile due to the multitude of comparisons between different controls conditions (passive, active, treatment as usual) and different exercise intensities and modalities (including the combination of therapies). However, this state of evidence is ideal for a systematic review with subsequent network meta-analysis. Network meta-analysis is designed to compare multiple treatment options or various versions of these treatments simultaneously. Publications 1 and 2 close this gap in the literature.

In healthy individuals, a single bout of aerobic exercise has a beneficial effect on sleep with small to moderate effect sizes [20]. Trials focused on patients with insomnia resulted in equivocal evidence, showing no or some beneficial effects of exercise on sleep [249–253]. However, no trials investigating the acute effects of exercise on sleep in patients with depression have been published to the author's best knowledge. Publications 3 and 4 address this research gap. In view of the evidence in patients with insomnia and healthy individuals, it was hypothesized that a single bout of 30 minutes of moderate-intensity aerobic exercise would improve sleep in patients with depression. The exercise duration was defined according to the current physical activity guidelines [198]. The target intensity (an average rate of perceived exertion of 13, i.e., moderate intensity [254]) was chosen based on the clinical experience that it is tolerable for all patients.

1.5.3 Exercise for arousal in patients with depression

The author is aware of only two studies that implemented regular exercise for patients with depression and assessed HRV as an outcome. Based on the data of Liu et al. [110], twenty-four weeks of Tai Chi improved HRV indices of older patients with depression. Toni et al. [111] concluded that 24 weeks of aerobic exercise combined with sertraline improved HRV more than sertraline alone in older patients with depression.

Multiple meta-analyses have established the positive effects of aerobic [21–23] and mind-body [255] exercise on HRV indices in healthy individuals across the lifespan. However, according to the meta-analysis of Bhati et al. [256], resistance exercise only improved HRV measures in people with disorders but not in healthy individuals.

According to sleep hygiene recommendations, exercise is conducive to sleep but should not be performed after 2 pm as this might increase arousal [257]. The only trials investigating the acute effects of exercise on nocturnal arousal were performed in predominantly young and healthy individuals. These trials resulted in somewhat mixed results, depending on the exercise program variables (i.e., intensity, duration, volume, timing during the day) and the training status of study participants [258–268]. However, none of the trials implementing 30 minutes of moderate-intensity exercise found evidence that the intervention altered nocturnal arousal. Consequently, it was hypothesized that a

single bout of moderate-intensity aerobic exercise performed multiple hours before bedtime would not alter nocturnal HRV. Considering the current sleep hygiene recommendations, the lack of evidence concerning the acute effects of exercise on arousal in patients with depression is problematic. Publications 3 and 5 address this research gap.

1.5.4 Exercise for depression- and insomnia-associated morbidity and mortality

The presence of subclinical [269] and clinical [32, 270] levels of depression increase the risk of mortality. However, there is a lack of evidence for a direct causal relationship between depression and mortality [270]. Poor sleep is also an independent risk factor for all-cause mortality and cardiovascular disease [271, 272]. Interestingly, *nocturnal* heart rate [273] and HRV [274, 275] are independent predictors for cardiovascular disease (i.e., even after adjustment for conventional risk factors).

There is a clear overlap between the purported pathophysiological mechanisms linking depression and insomnia with all-cause mortality and cardiovascular disease. These include reduced cardiorespiratory fitness as well as immune-inflammatory, oxidative, autonomic, and hypothalamus-pituitary-axis dysregulation (confer [276–278] for depression and [60, 279, 280] for insomnia). Of note, depression-associated inflammation is symptom-specific [281], and insomnia is one of the factors driving this relationship [282–285]. Empirical evidence from a cohort study shows that HRV partially mediates the relationship between cardiovascular disease outcomes and depression [286].

Regular aerobic exercise is a viable adjuvant therapy to improve cardiovascular disease outcomes in patients with depression, see Figure 2. Aerobic exercise improves inflammatory [287–289], oxidative [290], autonomic [111, 291], and hypothalamus-pituitary-axis [292] dysregulation as well as cardiorespiratory fitness [224] in patients with depression. Exercise also mitigates the relationship between poor sleep and mortality and cardiovascular disease [271, 293]. Lastly, higher cardiorespiratory fitness reduced the risk for cardiovascular mortality after being diagnosed with depression [207].

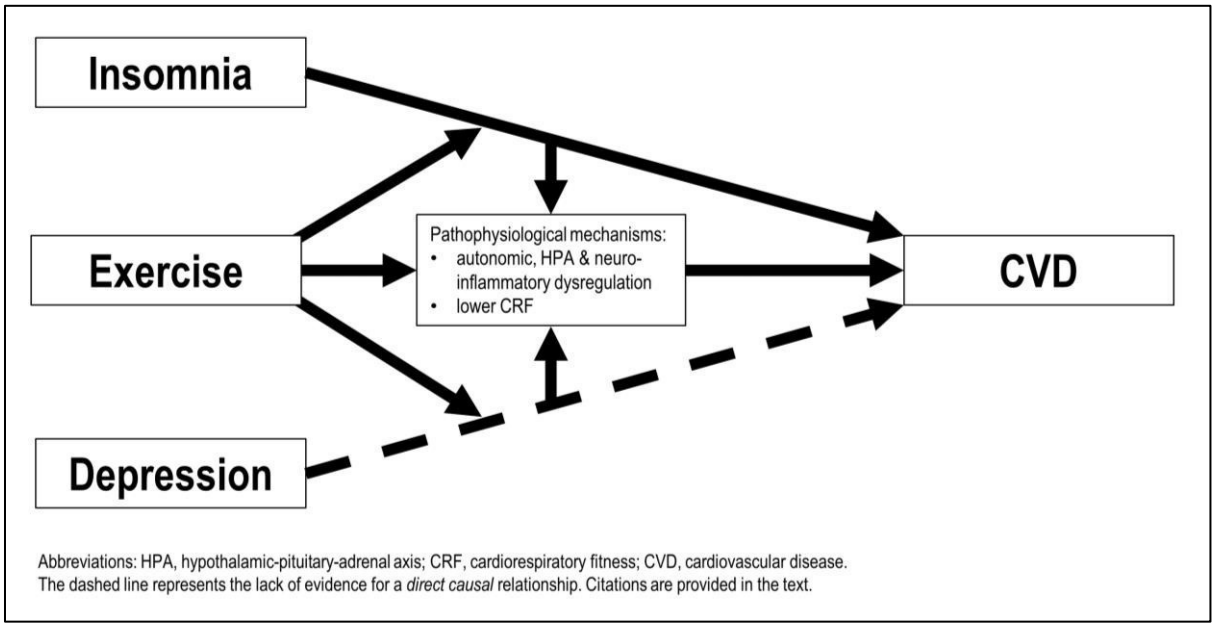

Figure 2: The influence of exercise on cardiovascular disease risk associated with insomnia and depression as well as potential pathophysiological mechanisms.

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Chapter 2

Aims and Hypotheses

2 Aims and Hypotheses

The overarching goal of this Ph.D. project is to improve our understanding of the effects exercise has on sleep and nocturnal arousal in patients with unipolar depression.

The specific goals of this Ph.D. project were:

- Aim 1: To summarize the existing research concerning the effects of aerobic, resistance, and mind-body exercise on sleep quality in patients with unipolar depression.
- Aim 2: To quantify the effect of a single bout of moderate-intensity aerobic exercise performed in the afternoon on sleep outcomes in patients with unipolar depression.
- Aim 3: To quantify the effect of a single bout of moderate-intensity aerobic exercise performed in the afternoon on mood and adverse effects.
- Aim 4: To quantify the effect of a single bout of moderate-intensity aerobic exercise performed in the afternoon on nocturnal and pre-sleep arousal.

The specific hypotheses of this Ph.D. project were:

- Hypothesis 1: Aerobic, resistance, and meditative movement exercise improves insomnia symptoms and subjective sleep quality in patients with unipolar depression.
- Hypothesis 2: An acute bout of moderate-intensity aerobic exercise improves objectively and subjectively measured sleep outcomes in patients with unipolar depression.
- Hypothesis 3: An acute bout of moderate-intensity aerobic exercise improves mood and does not increase adverse effects in patients with unipolar depression.
- Hypothesis 4: An acute bout of moderate-intensity aerobic exercise does not increase nocturnal and pre-sleep arousal in patients with unipolar depression.

Chapter 3

Publication 1: The effects of aerobic, resistance, and meditative movement exercise on sleep in individuals with depression: protocol for a systematic review and network meta-analysis

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Systematic Reviews

PROTOCOL Open Access

The effects of aerobic, resistance, and meditative movement exercise on sleep in individuals with depression: protocol for a systematic review and network meta-analysis

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Abstract

Background: The main objective of this review is to assess the effects of aerobic, resistance, and meditative movement exercise on sleep quality in patients with unipolar depression. A secondary goal is to ascertain the effects on sleep duration, sleepiness, daytime functioning, use of hypnotics, and adverse events.

Methods: A systematic computerized search will be performed in the following online databases: PubMed, EMBASE (on Ovid), Cochrane Library, PsycINFO (on Ovid), SPORTDiscus (on EBSCOhost), CINHAL (on EBSCOhost), Clinicaltrials.gov, WHO International Clinical Trials Registry, OpenGrey, and ProQuest Dissertations and Theses. Bibliographies of all included studies as well as any other relevant reviews identified via the search will be screened. Randomized trials using aerobic, resistance, or meditative movement exercise interventions which target sleep as a primary or secondary outcome will be included. The primary outcome will be differences in sleep quality at post-intervention. Secondary outcomes will be adverse events, differences in sleep duration, daytime sleepiness and functioning, and the use of hypnotics at post-intervention. Two authors will independently screen the identified records. Disagreement will be resolved by consensus or if no consensus can be reached by adjudication of a designated third reviewer. Data extraction will be done independently by two authors using a standardized and piloted data extraction sheet. Bias in individual studies will be assessed using the revised Cochrane risk of bias tool. The certainty of evidence across all outcomes will be evaluated using the CINeMA (Confidence in Network Meta-Analysis) framework. A frequentist network meta-analysis will be conducted. The systematic review and network meta-analysis will be presented according to the PRISMA for Network Meta-Analyses (PRISMA-NMA) guideline.

Discussion: This systematic review and network meta-analysis will provide a synthesis of the currently available evidence concerning the effects of aerobic, resistance, and meditative movement exercises on sleep in patients with unipolar depression. Thereby, we hope to accelerate the consolidation of evidence and inform decision-makers on potential benefits and harms.

(Continued on next page)

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(Continued from previous page)

Systematic review registration: The protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42019115705).

Keywords: Exercise, Aerobic, Resistance, Meditative movement, Depression, Sleep, Randomized, Trial, Systematic review, Network meta-analysis, Protocol

Background

Description of the condition

Worldwide lifetime prevalence of unipolar depression is estimated to be 10% [1]. Unipolar depression is the leading cause of burden of disease in middle- and high-income countries and is projected to become the leading cause worldwide by 2030 [2]. The economic burden of unipolar major depression alone was estimated to be $210 billion in the USA in 2010 [3]. In addition to the direct and often debilitating symptoms, unipolar depression also substantially increases the risk of all-cause mortality [4] and morbidity [5].

One of the diagnostic criteria for depression according to DSM-V [6] and ICD-10 [7] is disturbed sleep, i.e., insomnia or hypersomnia. This is reflected by the high prevalence (up to 90%) of co-occurring insomnia in individuals with depression [8]. Insomnia has a negative impact on health-related quality of life and daytime functioning [9, 10]. Moreover, sleep disturbances have been recognized as a mechanistic (i.e., causal or bidirectional) process in depression. Sleep problems are an independent risk factor for depression [11]. Depression and insomnia are linked in a bidirectional manner [12]. Comorbid sleep disorders have a negative influence on the disease trajectory in depressive disorders [13]. Some of the most prevalent residual symptoms after treatment response or remission in this clinical population are insomnia symptoms [14, 15]. This is pertinent because persistent sleep disorders increase the likelihood of relapse [13, 16, 17]. Sleep disorders are an independent risk factor for suicide [18, 19].

According to the British national (NICE) treatment guidelines, individuals with depression are to be treated with psychotherapy and pharmacotherapy [20]. However, antidepressants are of limited efficacy [21] and can cause considerable adverse effects. In a primary care setting the number needed to treat (NNT) for improvement of depressive symptoms by selective serotonin reuptake inhibitors is approximately seven whereas the number needed to harm (NNH) (withdrawal due to side effects) is estimated to be between 20 and 29 [22]. A combination of antidepressants and benzodiazepine receptor agonists (Z-drugs) in patients with depression, similarly, has been shown to be effective (NNT = 10) but causes considerable adverse events (NNH = 20) [23]. Due to the frequency of adverse side effects, non-adherence to antidepressants is high and associated with decreased remission rates, increased risk of relapse, and increased health care utilization [24]. Hypnotics are frequently prescribed for insomnia. However, they have a poor benefit-to-risk ratio with serious adverse effects including cognitive impairment, injury from falls and automobile accidents (including in younger individuals), cancer, suicide, and hypnotic withdrawal insomnia [25, 26]. In light of this evidence, interest in adjuvant and alternative therapies, especially exercise, has increased in the last decade.

Description of the intervention

The effects of exercise on depressive symptoms have been summarized in multiple meta-analyses [27–38]. Systematic reviews found moderate-to-large effect sizes for aerobic [28], resistance [36] as well as yoga [35] exercises on depression. Moreover, no significant differences between these interventions and antidepressant medication were found [28, 35]. The effect of other meditative movement exercises such as qi gong and tai chi seems to be positive, albeit less pronounced [37, 38]. Aerobic exercise interventions in depressive patients have also been found to improve cardiorespiratory fitness [27]. This is relevant because depression is known to increase the risk of cardiovascular mortality and morbidity [29, 30].

Current data suggest that exercise might be a suitable therapeutic option to improve sleep quality. Aerobic exercise has been shown to have positive acute (during the night immediately following exercise) and chronic (over several weeks) effects on sleep in healthy individuals with small-to-moderate effect sizes [39, 40]. These findings have been replicated in populations with sleep complaints [39, 41–43] and chronic disorders [44–49] and confirmed by a meta-analysis of previous meta-analyses [50]. A recent meta-analysis also found moderate-to-large effect sizes for mainly chronic resistance training on sleep quality [51]. Lastly, numerous meta-analyses show a positive effect of meditative movement on sleep quality in a variety of patient [49, 52] and elderly [53] populations. However, to the knowledge of the authors, no systematic review concerning the effect of exercise on sleep in patients with depression has been performed.

Potential mechanisms of action

Although the etiology of insomnia (with or without comorbidities) is not yet fully understood, hyperarousal is widely considered a causal and maintaining factor [54–56].

Multiple mechanisms of action, including ones which involve hyperarousal, have been proposed to explain the effect exercise has on sleep (confer the reviews of Buman and King (2010) [57] and Uchida et al. 2012 [58] for aerobic exercise). Insomniacs have been shown to have impaired thermoregulation [59]. Chronic exercise, on the other hand, improves thermoregulation [60, 61]. Increased skin temperature, which occurs during and immediately after acute aerobic [62], resistance [63], and meditative movement [61, 64] exercise, seems to modulate neural circuits in a way which might be conducive to sleep [65]. Exercise causes changes in the levels of pro-inflammatory cytokines [66], growth hormone [67, 68], and brain-derived neurotrophic factor [69–71] which seem to play a role in the regulation of sleep [72–74]. Aerobic [28], resistance [51], and meditative movement [75] exercise have positive effects on anxiety as well as depression and might thereby reduce psychophysiological arousal. Although it is not fully understood why humans sleep, one hypothesis states that humans sleep to optimize restorative processes [76]. Aerobic and resistance exercise increase energy expenditure and require muscle repair, thus stimulating such restorative processes. Aerobic exercise has also been shown to consistently produce phase shifts (i.e., changes in circadian rhythm within the 24 h cycle) in individuals of different ages and fitness levels. This effect has been found in individuals irrespective of age and cardiorespiratory fitness as well as independent from the effect of light. [77]. Therefore, aerobic exercise may act as a so-called 'zeitgeber' positively affecting entrainment (i.e., the synchronization of the endogenous and exogenous rhythms). It should be noted that it is unclear whether the mechanisms of action differ between insomniacs with and without psychiatric comorbidity.

Why it is important to do this review

The rationale for this review can be summarized in four points. (1) Sleep disturbances are of high prognostic relevance for remission in depression [11]. (2) Current therapies have a dissatisfactory benefit-to-risk-ratio. (3) Exercise has been shown to have positive effects on depression [28, 36, 75] as well as sleep [39, 41, 49, 51, 53]. (4) To the best of our knowledge, no systematic review has been performed to ascertain the effects of aerobic, resistance, and meditative movement exercise on sleep in people with depression.

The main objective of this review is to assess the effects of aerobic, resistance, and meditative movement exercise on sleep quality in patients with depression. A secondary goal is to ascertain the effects of exercise on sleep duration, sleepiness, daytime functioning, use of hypnotics, and adverse events (e.g., injuries, cardiovascular incidences).

Methods

Before initiation of the project, a search in relevant databases (including PROSPERO) showed no prior or ongoing systematic review of this subject. This systematic review protocol has been reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines [78] (see Additional file 1). Accordingly, the protocol for this study was published in the International Prospective Register of Systematic Reviews database (PROSPERO) [79] on 13th February 2019 (PROSPERO CRD420 19115705). Should any amendments to this protocol be necessary, they will be documented on the PROSPERO platform. The systematic review and network meta-analysis itself will be presented according to the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions [80].

Eligibility criteria

Population

Only studies on adult humans (>= 18 years old) of either sex with either a medical diagnosis of unipolar depression or presence of significant depressive symptoms as determined by a validated instrument (e.g., Beck Depression Inventory [81], Research Diagnostic Criteria [82], International Classification of Disease [7], or Diagnostic and Statistical Manual of Mental disorders [6]) will be included. Studies will be excluded if subjects had another substantial somatic disorder which might cause the depressive symptoms (i.e., primary symptoms are not depression) or if subjects were working night-shifts.

Intervention

Included trials must allocate subjects to at least one of the following: aerobic, resistance, or meditative movement exercise intervention. Aerobic exercise is defined as "any exercise that primarily uses the aerobic energy-producing systems, can improve the capacity and efficiency of these systems, and is effective for improving cardiorespiratory endurance" [83]. Resistance exercise is defined as "is exercise that causes muscles to work or hold against an applied force or weight" [84]. Meditative movement exercise is defined as a combination of some form of movement or body positioning, breathing, and relaxation [85]. The intervention can be acute (a single bout of exercise) or chronic (repeated exposure). We have not placed restrictions on the duration of the intervention period in order to include the maximum number of trials in this review. Potential statistical heterogeneity or inconsistency due to this factor will be explored (see below). No restrictions are placed on the setting (e.g., laboratory, outdoors), the social context (e.g., individual, group), or the level of supervision (e.g., not guided, under the supervision of an exercise

professional). Exercise can be part of a multicomponent intervention. Multicomponent interventions in which exercise was not a dominant part (i.e., exercise was one of four or more intervention modules) will be excluded.

Comparison

Trials have to allocate participants to aerobic, resistance, or meditative movement exercise vs. a comparison group. There are no restrictions on the comparison group (e.g., pharmacotherapy, psychotherapy, other exercise intervention).

Outcomes

Included trials must measure the effect of aerobic, resistance, or meditative movement exercise on sleep quality. This can be operationalized using self-reports or observer ratings.

Study type

In order to be eligible, trials must have employed randomized allocation.

Publication status

Studies are included regardless of whether or not they are published in a peer-reviewed journal. The use of unpublished trials in reviews is a controversial topic. Reviews have found that exclusion of gray literature may lead to an overestimation of effect size [86, 87]. On the other hand, van Driel et al. (2009) have shown that unpublished trials have poor or unclear methodological quality [88]. Therefore, methodological quality is considered when deciding whether the network meta-analysis is valid and if the number of studies allows it, subgroup analyses will include methodological quality.

Language

Articles written in English or German will be included. Articles in any other language will be included if a translation is made available. Any article which might be relevant, but could not be included due to the aforementioned language constraints will be listed in an appendix.

Information sources

Multiple sources will be used in this systematic review. A systematic computerized search will be performed in the following online databases: PubMed (on PubMed.gov), EMBASE (on Ovid), Cochrane Library (on cochranelibrary-wiley.com), PsycINFO (on Ovid), SPORTDiscus (on EBSCOhost), and CINHAL (on EBSCOhost). OpenGrey (on opengrey.eu) and ProQuest Dissertations and Theses A&I (on proquest.com) will be searched to include gray literature. Bibliographies of all included studies as well as any other relevant reviews identified via the search will be screened. Clinicaltrials.gov and WHO International Clinical Trials Registry will be searched in order to identify ongoing as well as unpublished studies. Due to lack of controlled vocabulary and restricted length of search strings on these websites, a modified query will be used. Authors of included studies will be contacted via e-mail in order to inquire whether they know of any other relevant publications. All databases will be searched from their inception to the search date.

Search strategy

The search strategy will be constructed using the PICOS (patient, intervention, comparison, outcome, study design) framework. The search string will be comprised of controlled vocabulary whenever possible and free text. These terms (including appropriate truncation) will be selected in an iterative scoping search using the PICOS approach as well as backward and forward chaining. The study design component will be identified using the "Cochrane highly sensitive search strategies for identifying randomized trials" [89] and translated according to the database. Terms within each group will be combined with a Boolean "OR" and groups will be combined using a Boolean "AND" command. The PubMed search strategy (see Additional file 2) was adapted according to the controlled vocabulary in each database (see Additional file 2). The search strategy has been reviewed by an information scientist from the Basel Medical University Library using the Peer Review of Electronic Search Strategies (PRESS) guideline [90]. Test searches have been performed in order to ensure the validity of the search string.

Study records

Data management

All records identified in the databases will be collected in the reference management software EndNote® X8 (Thomson Reuters, New York, NY). However, deduplication will be performed using the Systematic Review Assistant-Deduplication Module. This software has been shown to have superior sensitivity and specificity in the deduplication process when compared with EndNote [91].

Selection process

Upon deduplication, records will be screened in two stages. Firstly, the title and the abstract of all records will be screened against the aforementioned inclusion and exclusion criteria (possible assessments: no (an exclusion criterion is found in title or abstract), maybe or yes (inclusion and exclusion cannot be definitively assessed or study is deemed to fulfill all criteria). Secondly, full texts of all articles which were not excluded in the first stage will be reviewed to determine whether all relevant criteria are met. Both stages will be performed

independently by two reviewers (GB and TZS) who will not be blinded to any information (e.g., author, journal, institutions). We do not blind the reviewers, since there is empirical evidence that blinding has little to no effect in meta-analyses [92]. Disagreement will be resolved by consensus. If no consensus can be reached, disagreement will be resolved by adjudication of a designated third reviewer (AST). An online systematic review software, Covidence [93], will be used to judge eligibility, resolve issues, and document the screening processes.

Before the actual screening process begins, both reviewers will screen 50 randomly selected articles in order to assure an adequate inter-rater agreement (Cohen's kappa > 0.80). Should this goal not be reached, this process will be repeated until the defined level of agreement is reached. Inter-rater agreement will be reported using raw agreement in percent and Cohen's kappa since both have respective strengths and limitations [94]. Furthermore, the number of disagreements solved by discussion and arbitration by the third reviewer will be stated. A flow diagram according to the PRISMA guidelines [95] will illustrate the number and the reasons for excluded and included citations.

Data collection process

A standardized data extraction form will be created in Excel on the basis of the Cochrane Consumers and Communication Review Group's data extraction template [96] and the DECiMAL guide [97]. This form will be tested against a subset of studies found in the scoping search and adapted accordingly before data extraction. Both reviewers (GB and TZS) will extract data independently. Authors will be contacted should data be missing. (The corresponding author will initially be contacted via e-mail with one additional reminder e-mail, should there be no response within 2 weeks. Subsequently, the other authors will be contacted). Disagreement will be resolved by consensus upon consulting the original paper or if no consensus can be reached, disagreement will be resolved by adjudication of a designated third reviewer (AST). To avoid the inclusion of double publications of one study, authors, treatment comparisons, sample sizes, and outcomes of the included studies will be compared. We will include the publication which has the most information pertinent to the meta-analysis.

Data items

For the calculation of relative treatment effects group means, corresponding standard deviations and group sizes will be extracted primarily. In case one of these values was missing, other statistical data that can be converted into means and standard deviations will be extracted. Conversions will be calculated according to formulas provided, e.g., [98, 99]. If standard deviations cannot be calculated from the available study information, we will impute them using the standard deviations reported in the other included studies [100]. We will conduct sensitivity analyses excluding studies in which standard deviations had to be imputed. If the N was missing in the table of analysis, we will use the N of the descriptive statistics. If studies report medians and interquartile ranges, a normal distribution will be assumed, if not indicated otherwise, to convert these values to means and standard deviations [98]. If studies only report adjusted outcome values, data will be extracted, but sensitivity analyses will be calculated without these studies to check for possible bias. We plan to extract the effect size provided by the study authors only if no other information was available for effect size calculation. If it is not possible to impute appropriate measures for the calculation of effect sizes, and no effect sizes are reported we will contact the authors.

Among others, the following information will be extracted from each study:

- Information on the study itself (e.g., title, publication date, authors)
- Methods (e.g., objective, design, number of participants included in the analysis)
- Risk of bias assessment (Cochrane revised risk of bias tool) [101]
- Setting (non-clinical vs. clinical, inpatient vs. outpatient)
- Participants (i.e., mean age, inclusion and exclusion criteria, severity of depression, diagnostic tool)
- Intervention (i.e., frequency, intensity, duration, type of exercise)
- Comparisons (comparator conditions)
- Outcomes (primary and secondary outcomes, adverse events)
- Results (mean and standard deviation of outcomes pre- and post-intervention as well as follow-up)
- Self-report vs. observer rating
- Duration of follow-up

Outcomes and prioritization

The primary outcome will be standardized mean differences (SMD) of sleep quality at post-exercise-intervention and at the last available follow-up assessment, measured by self-reports (e.g., PSQI [102], ISI [103]) or clinician ratings (sleep-related HAM-D items [104]).

Secondary outcomes will be:

1. SMD of sleep duration at post-exercise intervention and at last available follow-up assessment (measured objectively or subjectively)
2. SMD of daytime functioning at post-exercise intervention and at last available follow-up assessment,

measured by self-reports (e.g., Insomnia impact scale [105])
3. SMD of sleepiness at post-intervention and at last available follow-up assessment, measured by self-reports (e.g., Epworth sleepiness scale [106])
4. SMD of hypnotics use at post-intervention and at last available follow-up assessment, measured by self-reports
5. SMD of any adverse events as defined by Good Clinical Practice guidelines [107] (e.g., pain, falls, injuries, dizziness, myocardial infarction)

The rationale for the selection of the primary outcome is that perceived sleep quality, i.e., difficulties initiating or maintaining sleep or early morning awakening is one of the main complaints in insomnia. Reduced sleep duration [108] and daytime impairments are a further important category of complaints, markedly increasing the perceived need for treatment [109]. Adverse events must be considered in order to inform decision-makers on the benefit-to-risk ratio of an exercise intervention.

Risk of bias in individual studies

The risk of bias will be evaluated independently by two reviewers (GB and TZS) at the study level. Disagreement will be resolved by consensus or if no consensus can be reached, disagreement will be resolved by adjudication of a designated third reviewer (AST). Bias will be assessed using the revised Cochrane risk of bias tool [101]. This tool assesses five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of outcomes, and (5) selection of reported interventions. The three possible judgments are possible: low risk, some concerns, and high risk of bias. A summary table of bias assessment on study level will be included in the publication. These assessments will contribute to the evaluation of overall confidence in the findings of the network meta-analysis using the CINeMA framework [110].

Data synthesis

Data will be synthesized descriptively. A summary table of included studies will entail information on the authors, population characteristics (diagnostic criteria, baseline severity of sleep quality, depression, age, and numbers), interventions (exposure in each group), outcomes measures used, and results (sleep quality, sleep duration). Network meta-analysis will be performed. Statistical (number of studies and heterogeneity of results), clinical (heterogeneous populations), and methodological (low quality of trials or follow-up duration) aspects will be considered to decide whether network meta-analysis is valid. If network meta-analysis results must be deemed methodologically inaccurate, a pairwise meta-analysis will be considered. Should a pairwise meta-analysis also not be possible, studies will be summarized narratively.

The package netmeta [111] for the open-source software environment R [112] will be used to calculate network meta-analyses within a frequentist framework.

A network will be created including all available jointly randomizable treatments. We assume that any patient that meets all inclusion criteria is likely, in principle, to be randomized to any of the interventions in the synthesis comparator set.

We will address the assumption of transitivity which underlies network meta-analysis [113], by (1) assessing whether the included interventions are similar across studies using a different design, and (2) checking whether the distribution of potential moderators is balanced across comparisons [114]. A priori we have defined depression severity, comorbidities, age, and gender as potential effect modifiers and will evaluate the comparability of the respective characteristics across comparisons qualitatively.

We expect considerable diversity of outcome measures and will, therefore, calculate standardized mean differences (SMD) using Hedge's g with 95% confidence intervals [115]. SMD is the mean difference between groups divided by the pooled standard deviation. The effect size measure allows comparison of effect sizes across similar measurements of a single outcome. The conventional and somewhat arbitrary classification of SMD proposed by Cohen (1988) [116] has been expanded to include very small (.01), small (0.2), medium (0.5), large (0.8), very large (1.2), and huge (2.0) effect sizes [117]. Random-effects pairwise SMDs across studies will be calculated based on the available comparisons between treatment and comparator treatments [118]. Inverse variance weighting is used for pooling. In addition, indirect evidence will be estimated using the entire network of evidence. Random-effects netmeta accounts for dependencies between comparisons in case of multi-arm trials [119]. The command pairwise will be used in case of multi-arm trials, in order to transform the dataset to the comparison level, which is needed for conducting the network meta-analysis.

The primary outcome will be SMD of sleep quality assessed via self- or observer-reported measures. If more than one primary outcome is reported, the most frequently used scale will be included in the analysis to reduce between-study heterogeneity. If possible, we will assess the association between instruments and changes in sleep quality. Two individual analyses will be run for the outcome data at the end of treatment, and the last available follow-up. Separate network meta-analyses will be conducted for secondary outcomes if possible. Results from network meta-analysis will be presented as summary SMD for each possible pair of treatments.

Whenever possible, measures of uncertainty will be reported in the form of the 95% confidence interval and 95% prediction interval.

To calculate statistical heterogeneity between studies on the pairwise level, the Q statistic will be used [89]. Further τ^2 will be analyzed to estimate the variance caused by the distribution of the true study means [120]. I^2 will be evaluated to indicate the amount of observed variance that can be attributed to between-study heterogeneity [121]. I^2 and the corresponding confidence interval can be interpreted as the percentage of overall heterogeneity that is due to variation of the true effects. An I^2 value of 0% to 40% might not be important, 30 to 60% may represent moderate heterogeneity, 50 to 90% may represent substantial heterogeneity, and 75 to 100% considerable heterogeneity [89]. In NMA, we will assume a common estimate for the heterogeneity variance across the different comparisons.

Local and global methods will be used to detect inconsistency [122]. The presence of inconsistency will be evaluated using the following approaches: (1) locally using the netsplit command (i.e., testing the difference between estimates derived from direct evidence and estimates derived from indirect estimates for statistical significance) and (2) globally using the decomp.design command (i.e., using the design-by-treatment interaction model). For this purpose, the total Q statistic (i.e., the measure of total heterogeneity/inconsistency in the network) will be decomposed to an inconsistency factor (between designs) and a heterogeneity factor (within designs). We will compare the magnitude of heterogeneity between consistency and inconsistency models to determine how much heterogeneity will be explained by inconsistency. We will do this by testing the residual inconsistency, which remains under the assumption of a full design by treatment interaction model for statistical significance.

In the case of statistical heterogeneity or inconsistency between results from individual studies, we will investigate the potential impact of the following trial-level effect modifiers: (1) year of publication, (2) study precision (i.e., sample size), (3) studies reporting non-adjusted vs. adjusted means, (4) studies with imputed standard deviations vs. studies which reported standard deviations. If the number of studies allows it, theoretically driven subgroup analyses will be done according to population (e.g., severity of depression), duration of intervention, duration of follow-up, outcome characteristics (i.e., self- vs. observer ratings, objective vs. subjective sleep duration), and methodological quality.

Meta-biases and confidence in cumulative evidence

The confidence in the network meta-analyses will be estimated using the Confidence in Network Meta-Analysis (CINeMA) framework [110]. This includes study limitation, indirectness, inconsistency (heterogeneity, incoherence), imprecision, and publication bias. Publication bias will be assessed according to the GRADE guideline [123] and by comparing eligible trials identified in registries (e.g., clinicaltrials.gov) with published data. Selective reporting bias will be assessed by comparing protocols (if available) and reports of trials.

Dissemination

The results will be published in a peer-reviewed journal and presented at conferences as well as invited talks.

Discussion

This systematic review will provide an overview of the current state of evidence concerning the effects of aerobic exercise on sleep in patients with depression. To the best of our knowledge, this will be the first systematic review concerning this topic. The primary outcomes analyzed will provide evidence on the benefits, i.e., duration and perceived quality of sleep, as well as serious harms. Secondary outcomes will provide information on sleep-related constructs such as daytime functioning and sleepiness as well as other adverse outcomes. Furthermore, gaps in the current literature will be identified, and recommendations for future avenues of research will be given. Strengths of this systematic review include the search in multiple databases according to the interdisciplinary nature of the subject, the systematic approach including screening, data extraction, and quality assessment by two independent reviewers, as well as transparency in reporting according to guidelines. The main limitation is the language restriction to German and English which might lead to language bias. Considering the importance of sleep disturbances in depression, we hope that this systematic review can accelerate the consolidation of evidence, such that decision-makers (patients, health-care professionals, and policy-makers) are provided with high-quality evidence to facilitate decisions on whether and how to implement aerobic, resistance, or meditative movement exercises as a treatment module for patients with depression.

Current stage of systematic review

PROSPERO stage 1, preliminary searches completed.

Additional files

Additional file 1: Completed PRISMA-P Checklist. (PDF 345 kb)

Additional file 2: Search strategy for PubMed, EMBASE, PsycINFO, Cochrane Library, SportDiscus, CINAHL, OpenGrey, ProQuest Dissertations and Theses, Clinicaltrials.gov, and International Clinical Trials Registry Platform. (PDF 277 kb)

Abbreviations

CINeMA: Confidence in Network Meta-Analysis; PICOS: Patient, intervention, comparison, outcome, study design; PRESS: Peer Review of Electronic Search

Strategies guideline; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for systematic review protocols; PROSPERO: International prospective register of systematic reviews; SMD: Standardized mean difference

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Authors' contributions
GB, HG, MW, TZS, DS, HP, MG, RvK, and AST contributed to the design, revised the manuscript, and approved the final manuscript. GB conceived the study, defined the search strategy, drafted the manuscript, registered the protocol with PROSPERO, and managed the overall project. HG conceived the analysis and helped write the protocol. MW reviewed the search strategy using the PRESS guideline.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Gavin Brupbacher is funded through an industry-sponsored PhD, provided by Oberwaid AG, St. Gallen, Switzerland. Dr. Doris Straus and Dr. Hildburg Porschke are employed by Oberwaid AG. Arno Schmidt-Trucksäss and Roland von Känel are on the scientific advisory board of the Oberwaid AG. All other authors declare no competing interests.

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Chapter 4

Publication 2: The effects of exercise on sleep in unipolar depression: a systematic review and network meta-analysis

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CLINICAL REVIEW

The effects of exercise on sleep in unipolar depression: A systematic review and network meta-analysis

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SUMMARY

Insomnia predicts the onset, course, and reoccurrence of unipolar depression. However, systematic reviews of treatment options for insomnia in unipolar depression are lacking. After screening 7725 records, 17 trials comprising 1645 patients randomized to 13 treatments were included for quantitative synthesis. Network meta-analysis showed that compared to a passive control condition, all exercise interventions except moderate aerobic exercise alone resulted in significantly better sleep outcomes. Compared with treatment as usual, mind-body exercise plus treatment as usual (SMD: −0.46; 95% CI: −0.80, −0.12) and vigorous strength exercise (SMD: −0.61; 95% CI: −1.12, −0.10) were significantly more effective. Pairwise meta-analyses showed that mind-body exercise (SMD: −0.54; 95% CI: −0.85, −0.23) had beneficial effects compared to passive control. The network meta-analysis is statistically very robust with low heterogeneity, incoherence, and indirectness. However, confidence in the findings was moderate to very low, primarily due to within-study bias. This is the first network meta-analysis to assess exercise's efficacy to improve sleep quality in patients with depression. The findings confirm the benefits of exercise as an add-on treatment for depression. This consolidation of the current state of evidence can help clinicians make evidence-based decisions.

Introduction

Insomnia symptoms and insomnia disorder predict the onset, course, and recurrence of unipolar depression and unipolar depressive symptoms. Three meta-analyses of prospective cohort studies show that insomnia symptoms and insomnia disorder more than double the risk of developing clinical or subclinical depression [1–3]. Insomnia symptoms have a detrimental effect on treatment trajectory by reducing responsiveness to psychotherapy [4], pharmacotherapy, or a combination of these [5–7]. Sleep disturbances are the most frequent residual symptoms after remission of a depressive episode [8,9]. They increase the risk for [10] and seem to be a prodromal symptom of relapse [11]. Insomnia disorder also increases the risk of treatment-resistant depression [12]. Insomnia symptoms co-occurring with depression increase the risk of suicide [13] and are associated with myocardial infarction [14]. Sleep disturbances are associated with a lower quality of life [15], role impairment [16], and the need for disability retirement in patients with depression [17]. Treatment of insomnia in patients with depression is, therefore, of paramount importance. Current treatment guidelines for unipolar depression recommend psychotherapy and pharmacotherapy [18]. However, symptoms of insomnia persist in approximately half of the patients who respond to psychotherapy or

Abbreviations: CBT-I, cognitive behavioral therapy for insomnia; HE, health education; SMD, standardized mean difference; TAU, treatment as usual.

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pharmacotherapy for depression [19]. Moreover, co-therapy for depression and insomnia leads to better outcomes than monotherapy for depression [20]. Treatment guidelines for insomnia specifically recommend cognitive behavioral therapy for insomnia (CBT-I) and pharmacotherapy [21]. However, meta-analyses have shown that although CBT-I improves subjective sleep quality [22], CBT-I does not improve polysomnography-defined sleep parameters [23]. Furthermore, CBT-I is often not available due to the limited number of trained specialists. Hypnotics have a dissatisfactory benefit-to-risk-ratio [24], and patients often prefer non-pharmacological treatment [25,26]. Therefore, further add-on therapies to treat insomnia in patients with depression are needed.

Exercise may be such a potential candidate. Exercise performed to treat depression can mostly be categorized into aerobic, resistance, or meditative movement exercises. Aerobic exercise involves large muscle groups and consists of repeated movement patterns that primarily use aerobic energy-producing systems [27]. Resistance exercise entails muscles working against an applied force or weight [28]. Mindy-body exercises are characterized by slow movements or body positioning, often combined with breathing and relaxation [29]. Multiple mechanisms of action might explain the effect exercise has on sleep. Insomnia is associated with impaired thermoregulation [30,31], while regular exercise seems to improve it [32,33]. Acute aerobic [34], resistance [35], and mind-body exercise [36] increase skin temperature, which is conducive to sleep [37]. Acute exercise also increases the levels of circulating pro-inflammatory cytokines [38], growth hormone, and brain-derived neurotrophic factor, which are involved in sleep regulation [39]. Aerobic [40], resistance [41], and meditative movement [42] exercise decrease psycho-physiological arousal by reducing anxiety and depression. Indeed, aerobic [43–45], resistance [41], and meditative movement exercises improve sleep quality [46–48] in non-depressed individuals.

The rationale for this review is based on five premises. 1) Insomnia is highly relevant to the treatment of depression. 2) Current therapies have a dissatisfactory benefit-to-risk-ratio, and many patients prefer non-pharmacological therapies. 3) There is evidence that exercise positively affects insomnia. 4) To the best of our knowledge, there is no systematic review on this topic focusing on patients with depression. 5) Network meta-analysis is more informative compared to a conventional pairwise meta-analysis in situations where more than one treatment option is available for a particular clinical condition or if treatments are implemented in various versions (e.g., different intensities or including different additional treatment components). Thus, the primary aim of this systematic review and network meta-analysis was to assess the effects of aerobic, resistance, and meditative movement exercise on sleep quality in patients with depression. The secondary aim was to compare the effects of exercise treatments with the recommended established treatments for insomnia (including medication and psychotherapy) as well as with no treatment and active control comparators.

Methods

We prospectively registered this systematic review in the International Prospective Register of Systematic Reviews database (PROSPERO) on February 13th 2019 (PROSPERO CRD42019115705). A detailed study protocol is available [49]. The only deviation from the protocol was that we assessed the risk of bias in individual trials using the original Cochrane tool [50] instead of the 2.0 version [51] since the new version was not yet implemented in Covidence [52]. This report follows the PRISMA network meta-analysis extension [53] and AMSTAR2 guidelines [54].

Eligibility criteria

We included trials which met the following criteria: 1) participants were adults (i.e., 18 years or older) of either sex 2) with a diagnosis or significant symptoms of unipolar depression (determined according to a validated instrument, e.g., ICD-10, Beck Depression Inventory; in case of self-reported questionnaires baseline values had to be above the remission cut-off), 3) participants were treated with either aerobic, strength or meditative movement exercise, 4) the trial included at least one other comparator group, 5) the trial reported sleep quality as an outcome, 6) the trial employed randomized allocation, and 7) the trial was reported in English or German. We assessed the eligibility of treatments using the following definitions. Aerobic exercise is defined as any exercise that mainly used aerobic energy-producing systems and improves cardiorespiratory fitness [27]. Resistance exercise is defined as “exercise that causes muscles to work or hold against an applied force or weight” [28]. Meditative movement exercise is defined as a combination of some form of movement or body positioning, breathing, and relaxation [29]. Sleep quality was defined as insomnia symptoms and sleep disturbances measured with questionnaires. Based on the scoping search, we were confident that a restriction to randomized controlled trials would not limit the review on this topic.

We excluded trials if participants 1) were working night-shifts or 2) suffered from a significant somatic disorder, which might cause depressive symptoms. We placed no restrictions on publication status (i.e., peer-reviewed or grey literature), duration, setting (e.g., indoor), social context (e.g., group exercises), or level of supervision of the intervention.

Data collection

We performed a systematic computerized search of the following online databases from their inception to the search date: PubMed (on PubMed.gov), EMBASE (on Ovid), Cochrane Library (on cochranelibrary-wiley.com), PsycINFO (on Ovid), Sportdiscus (on EBSCOhost), CINHAL (on EBSCOhost), OpenGrey (on opengrey.eu), ProQuest Dissertations & Theses A&I (on proquest.com), Clinicaltrials.gov and WHO International Clinical Trials Registry on April 24th, 2019 and updated the search on February 12th, 2020. We checked the bibliographies of all included studies as well as any other relevant reviews for further relevant trials. Lastly, we contacted all authors of the included studies via e-mail in order to inquire whether they knew of any other relevant publications.

The search strategy was reviewed by an information scientist from the Basel Medical University Library using the Peer Review of Electronic Search Strategies (PRESS) guideline [55]. Supplementary file 1 section one provides the search strings for each database.

Identified records were managed using EndNote® X8 (Thomson Reuters, New York, NY) and Systematic Review Assistant-Deduplication Module [56]. We screened the deduplicated records independently by two reviewers (GB and TZS) in two stages (title and abstract as well as full text) using Covidence [52].

Both reviewers (GB and TZS) extracted data independently. Disagreements were resolved by consensus. We contacted the authors if necessary data was not reported (see supplementary file 1 section 2).

The primary outcome was the standardized mean difference (SMD) of sleep quality assessed via self- or observer reported questionnaires at post-intervention. Secondary outcomes were sleep quality at follow-up, objectively (polysomnography, accelerometry) or subjectively (sleep logs, questionnaires) measured sleep duration, daytime functioning, daytime sleepiness, hypnotics use, and adverse events. We also extracted information on

population characteristics (gender, age, depression severity at baseline) and potential moderators (e.g., intervention modalities, concomitant therapy).

Analyses

The geometry of the network was explored graphically (using the *netmeta* package [57]), qualitatively (summary of population and intervention characteristics per node), and quantitatively (number of included trials, interventions, and comparisons). Two reviewers (GB and TZS) independently evaluated the risk of bias at the study level using the Cochrane risk of bias (RoB) tool [50]. These assessments contributed to the evaluation of overall confidence in the findings, which was evaluated using the CINeMA framework [58].

We expected considerable diversity of outcome questionnaires and, therefore, calculated SMD using Hedge's g with 95% confidence intervals. We performed the analyses using R version 3.6.3 [59] and the package *netmeta* [57], which accounts for dependencies between comparisons in the case of multi-arm trials. Random-effects pairwise SMDs were calculated based on the available comparisons between treatment and comparator treatments. Inverse variance weighting was used for pooling. Results from network meta-analysis are presented as summary SMD with 95% confidence and prediction intervals. Also, we conducted random-effects pairwise meta-analyses for all comparisons with two or more studies.

The definition of nodes in a network meta-analysis is not trivial. However, we are confident to have defined treatment nodes in a clinically meaningful way and such that transitivity holds. We have listed effect modifiers (age, gender, baseline depression severity, intervention characteristics, and outcome measures) as predefined in our protocol [49] by node in the supplementary file 2 section 1. We combined all interventions which are currently recommended by guidelines (i.e., psychotherapy, pharmacotherapy, general practitioner care) into the node 'treatment as usual'. The node 'active control' contains treatments that control for non-specific effects, e.g., placebo or group dynamics. 'Passive control' refers to wait-list or no-treatment groups. 'Mind-body exercise' refer to yoga, qi gong or tai chi interventions. 'Light intensity strength' includes resistance training at maximal 50% of one-repetition maximum. 'Vigorous-intensity strength' refers to interventions in which intensity was set to 80% of one-repetition maximum. Aerobic exercise was classified according to the definition of Norton et al., 2010 [60]. 'Moderate aerobic exercise' includes the following intensities: 55 < 70% of maximal heart rate, 40 < 60% of heart rate reserve, or RPE 11–13. 'Vigorous aerobic exercise' includes interventions at 70 > 90% of maximal heart rate, 60 < 85% of heart rate reserve, or RPE 14–16.

Further details on data preprocessing (e.g., imputation, data extraction from graphs) as well as network meta-analysis and sensitivity analyses can be found in the supplementary file 2 section 2 and supplementary file 2 section 9, respectively.

Results

Our systematic search identified 10,361 records. We included an additional record [61] based on feedback from authors of included trials. After deduplication, 7725 studies were identified for title and abstract screening and 337 articles were identified for full-text review. A list of all studies excluded at the full-text level, including the reasons therefore, is provided in the supplementary file 1 section 4. Interrater-agreement was good at both title and abstract (Cohen's Kappa: 0.61; percentage agreement: 97%) as well as full text (Cohen's Kappa: 0.81; percentage agreement: 97%) level. A total of 17 trials [61–77] met our inclusion criteria (see Fig. 1).

These 17 trials yielded post-intervention sleep quality measures for our analyses, including a total of N = 1645 patients, which had been randomized to 13 treatments yielding 35 comparisons. Average baseline depression severity was mostly moderate [63–65,71,73,74,76,77] or mild [62,69,70,72,75] based on symptom questionnaires. The remaining trials included patients with severe depression at baseline [68] or only reported that included patients scored above clinical cut-offs in validated unipolar depression questionnaires [61,66,67]. The median of mean age was 47 (range: 25.6–71.3) years. Three trials included older patients only (≥60 years) [70,75,76]. Four studies were conducted among women only [62,66,67,74]. The median number of patients per trial was N = 54 (range: 28–472). Patients were allocated to some form of control intervention (all forms: N = 870; treatment as usual: N = 532; active control: N = 94; passive control: N = 244), exercise (all forms: N = 764; aerobic exercise: N = 390; strength exercise: N = 62; mind-body: N = 312) or meditation (N = 11). The meditation group was included as a comparator in our network, since one trial [72] randomized patients to one of four groups: low intensity strength exercise, passive control, meditation, and active control. Treatment as usual (psychotherapy, pharmacotherapy, a combination of both, or general practitioner care) was the most frequent comparator [63–65,69,70,73,76,77], followed by passive control [61–63,66,67,71,72] and mind-body exercise [61,62,66,71,74,77] (see Fig. 2). The median group size per allocation was N = 24 (range: 11–315). The median intervention duration was 12 weeks (range: 4–16 weeks). Most exercise interventions were either fully (71%) or partially (25%) supervised, while only 4% were unsupervised. Interventions were most frequently delivered in a group format (group: 46%, mixed: 17%, individual: 17%, not reported: 21%). Self-report questionnaires were the most frequently reported outcome measure (Pittsburgh sleep quality index: 47%, other self-reports: 35%). Trials were conducted in the USA (N = 7), Europe (N = 3), China (N = 3), Australia (N = 2), Canada (N = 1), and Brazil (N = 1). None of the trials reported sleep quality as a primary outcome. Sources of funding for each trial are listed in the supplementary file 2 section 3. More detailed baseline descriptive statistics are given in the supplementary file 2 section 4. Secondary outcomes were underreported. Sleep duration [75], daytime functioning [63], and daytime sleepiness [62] were each reported by one study, whereas hypnotic use was not reported by any trial. Adverse events were reported only by three trials [62,70,76]. Sleep quality at follow-up was reported only by four trials [61,72,74,77]. Hence, we did not perform a network meta-analysis for these secondary outcomes. We observed a high risk for overall risk of bias in individual trials (see supplementary file 2 section 5). The highest risk of bias stems from a lack of blinding participants, personnel, and outcome assessors. Concerning the remaining four risk of bias indicators, a lack of information was observed in many studies. Therefore, the actual risk for the presence of biases in the included studies remains mostly unknown.

Figs. 3, 4, and Table 1 present the results of the random effects-network meta-analysis based on 17 trials. All exercise interventions, except moderate aerobic training (SMD: −0.31; 95% CI: −0.62, 0.00) and meditation (SMD: −0.31; 95% CI: −0.99, 0.37), were more effective in improving sleep quality when compared to passive control. Active control, mind-body exercise, treatment as usual, and vigorous aerobic exercise resulted in similar effects. Combining mind-body exercise (SMD: −0.44; 95 %CI: −0.65, −0.24) with treatment as usual (SMD: −0.48; 95% CI: −0.75, −0.22) showed an additive effect (SMD: −0.94; 95% CI: −1.35, −0.54) compared to passive control. Mind-body combined with treatment as usual (SMD: −0.46; 95% CI: −0.80, −0.12) and vigorous strength

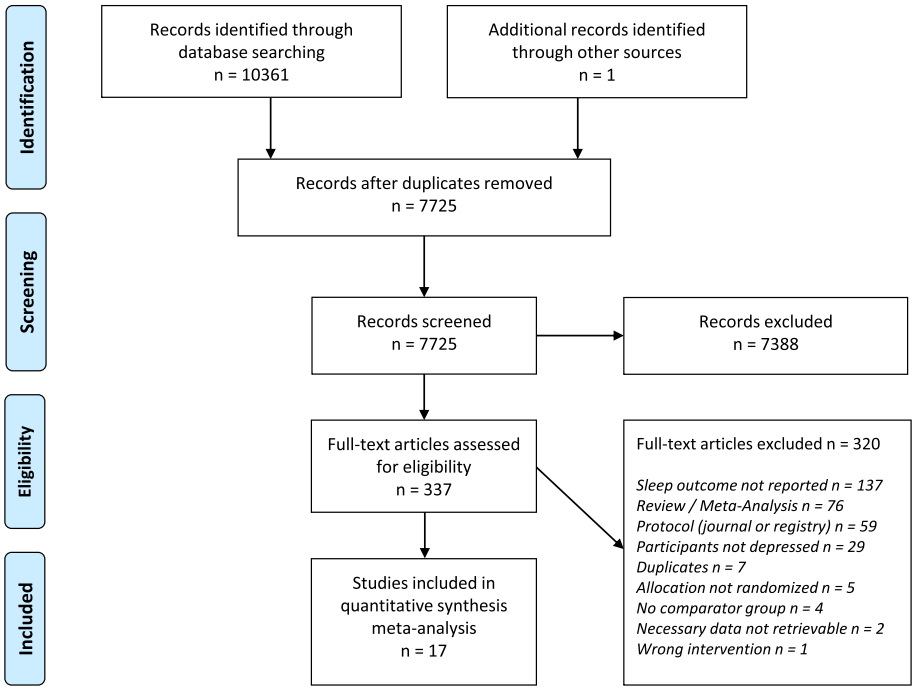

Fig. 1. PRISMA flow diagram of systematic search and included trials.

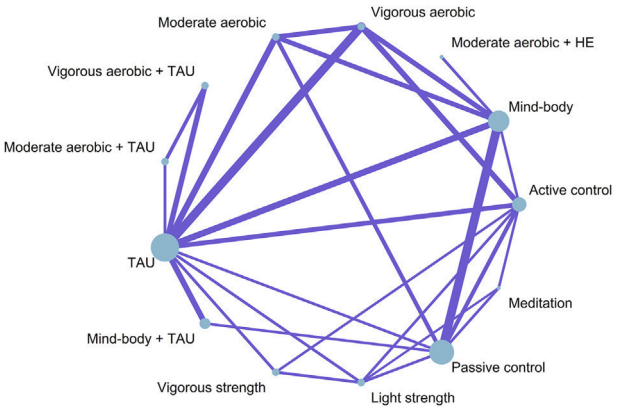

Fig. 2. Network geometry of eligible comparisons for sleep quality. Note: node size corresponds to the number of trials; line width corresponds to the inverse standard error; abbreviations: HE = health education; TAU = treatment as usual.

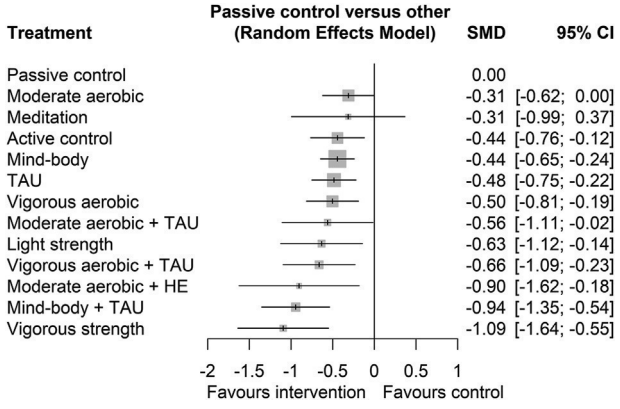

Fig. 3. Forest plot of network meta-analysis estimates of passive control vs. other interventions for sleep quality Abbreviations: HE = health education; TAU = treatment as usual.

(SMD: −0.61; 95% CI: −1.12, −0.10) were the only treatments which were superior when compared to treatment as usual (see Fig. 4 and Table 1). Global heterogeneity was low ($\tau^2 = 0.003$; $I^2 = 4.3\%$ [0.0%; 56.9%]), and there was no evidence for local (see supplementary file 2 section 6) or global inconsistency in the model under the assumption of a full design-by-treatment interaction random-effects model, Q (10) = 3.27, $p = 0.97$.

Standardized mean differences at post-intervention between all comparators of each included trial are presented in the supplementary file 2 section 7. No publication bias was detected and confidence in the evidence was moderate (43% of comparisons), low (39% of comparisons), or very low (18% of comparisons), see supplementary file 2 section 8. Average indirectness was low for most comparisons, see supplementary file 2 section 1. We conducted multiple sensitivity analyses as predefined in our protocol and mentioned above. All findings were confirmed; however, some effect sizes substantially increased when restricting analyses to trials which only included participants if they had a formal diagnosis of depression (i.e., according to DSM or ICD), see supplementary file 2 section 9. A juxtaposition of direct, indirect, and network effect estimates as well as prediction intervals are presented in the supplementary file 2 section 10. We did not perform any subgroup analyses since very low levels of between-study heterogeneity suggest the absence of effect modifiers (see supplementary file 2). The results of pairwise meta-analyses are presented in Fig. 5.

Discussion

Principal findings

In this systematic review and network meta-analysis, we compared the effects of aerobic, resistance, and mind-body exercises on sleep quality in patients with depression. This systematic

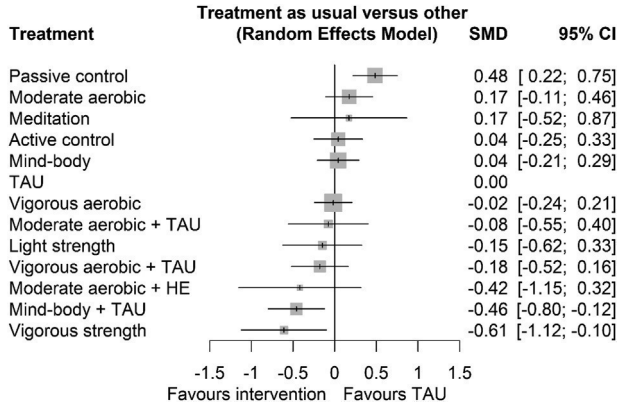

Fig. 4. Forest plot of network meta-analysis estimates of treatment as usual vs. other interventions for sleep quality. Abbreviations: HE = health education; TAU = treatment as usual.

review is based on 17 trials, which included 1645 patients randomly assigned to 13 comparators. None of these studies reported objective sleep measurements, which means that current evidence can only relate to subjective sleep quality. We found that all treatments but moderate aerobic exercise alone and meditation outperformed passive control. Combining mind-body exercise with treatment as usual had an additive effect. Vigorous strength exercise and mind-body exercise in combination with treatment as usual were the only two treatments that were more efficacious than treatment as usual alone. None of the exercise interventions was significantly less efficacious than treatment as usual. Our results indicate that besides the recommended first-line treatments, various additional treatment options appear similarly beneficial in improving sleep quality in depressed patients. This finding may be particularly pertinent to health care providers when making treatment decisions.

Comparison with other studies

To our knowledge, this is the first systematic review and network meta-analysis of the effects of exercise on indicators of sleep quality in patients with depression. Previous reviews and meta-analyses have assessed the effect of exercise on sleep. However, it remains unclear whether these previous findings are directly applicable to sleep problems in the specific population of patients with depression. Reviews focused on populations that were either very heterogeneous (e.g., individuals with and without specific disorders [41,45] or patients with different mental disorders [78]), had insomnia but no depression [43,79], or were healthy individuals [80]. An additional limitation of previous reviews is that they did not differentiate between aerobic, resistance, and mind-body exercises when comparing exercise with passive control or other treatments [43,78,80–83].

Previous analyses on aerobic exercise included individuals who were healthy, had sleep problems, or had cancer [45,82,83]. Despite these vastly different populations, our findings are similar, albeit with somewhat smaller effect sizes. Kovacevic et al. [41] is the only other meta-analysis that specifically focused on resistance exercise interventions. We found slightly larger effect sizes in our meta-analytic sample, especially for vigorous strength. Five meta-analyses have previously reported the effects of mind-body exercise. While three [46,82,84] effect size estimates are consistent with our findings, two [80,85] reported larger effect sizes. Meta-analyses that did not differentiate exercise type [43,78,80–83] generally found similar effect size estimates, except in Mercier et al. [86]. However, they only included patients with cancer, which might explain the discrepancy.

Meta-analyses show that the effect sizes of hypnotics compared to placebo (tricyclic antidepressants: SMD -0.39, 95% CI: −0.56, −0.21; trazadone: SMD -0.34, 95% CI: −0.66, −0.02) [87] and CBT-I compared to non-active control (Pittsburgh sleep quality index: Hedge's g = −0.65, 95% CI: −0.51, −0.79; Insomnia severity

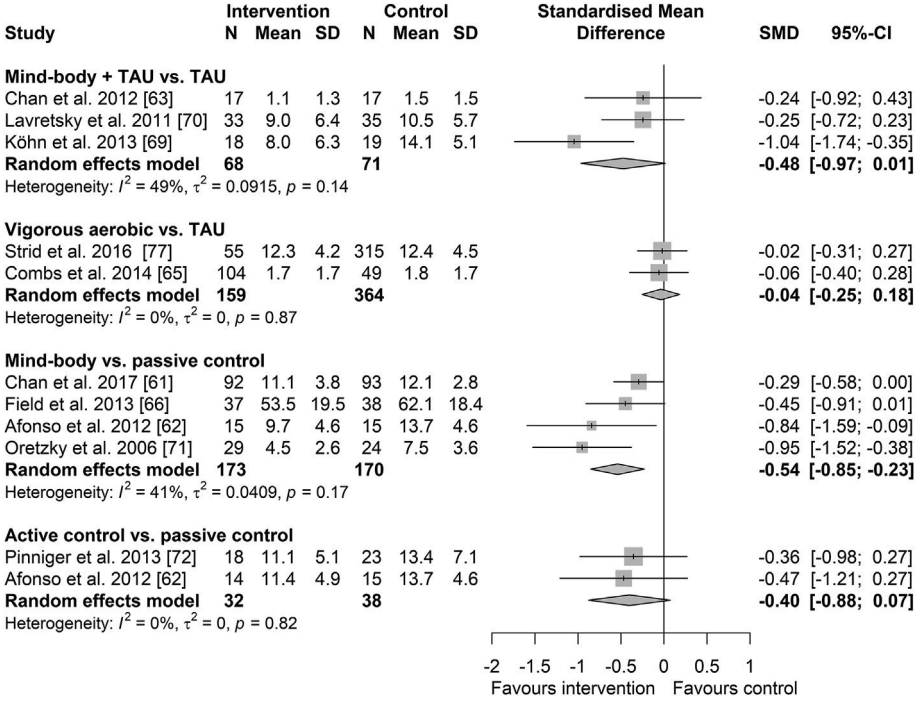

Fig. 5. Forest plot of pairwise meta-analysis estimates for sleep quality Abbreviations: TAU = treatment as usual.

Table 1
League table with network (lower diagonal) and direct (upper diagonal) evidence.

active control	-0.02 [-0.76; 0.72] k = 1; τ² = NA	-0.13 [-0.88; 0.63] k = 1; τ² = NA	0.35 [-0.39; 1.09] k = 1; τ² = NA	.	.	.	.	-0.40 [-0.88; 0.07] k = 2; τ² = 0.000	-0.06 [-0.47; 0.35] k = 1; τ² = NA	0.00 [-0.36; 0.36] k = 1; τ² = NA	.	**0.81** **[0.03; 1.60]** **k = 1; τ² = NA**
0.19 [-0.30; 0.68] k = 17; τ² = 0.003	light strength	-0.11 [-0.93; 0.72] k = 1; τ² = NA	.	.	.	.	.	-0.30 [-1.01; 0.41] k = 1; τ² = NA	-0.38 [-1.05; 0.29] k = 1; τ² = NA	.	.	0.25 [-0.42; 0.93] k = 1; τ² = NA
-0.13 [-0.82; 0.56] k = 17; τ² = 0.003	-0.32 [-1.07; 0.43] k = 17; τ² = 0.003	meditation	.	.	.	.	.	-0.20 [-0.93; 0.53] k = 1; τ² = NA	.	.	.	.
0.00 [-0.32; 0.33] k = 17; τ² = 0.003	-0.19 [-0.69; 0.31] k = 17; τ² = 0.003	0.13 [-0.56; 0.82] k = 17; τ² = 0.003	mind-body	.	-0.04 [-0.45; 0.36] k = 1; τ² = NA	0.46 [-0.23; 1.15] k = 1; τ² = NA	.	**-0.54** **[-0.85; -0.23]** **k = 4; τ² = 0.041**	0.11 [-0.20; 0.42] k = 1; τ² = NA	0.13 [-0.26; 0.52] k = 1; τ² = NA	.	.
0.50 **[0.06; 0.94]** **k = 17; τ² = 0.003**	0.31 [-0.26; 0.89] k = 17; τ² = 0.003	0.63 [-0.13; 1.39] k = 17; τ² = 0.003	**0.50** **[0.10; 0.91]** **k = 17; τ² = 0.003**	mind-body + TAU	.	.	.	**-1.03** **[-1.76; -0.29]** **k = 1; τ² = NA**	-0.48 [-0.97; 0.01] k = 3; τ² = 0.092	.	.	.
-0.13 [-0.50; 0.24] k = 17; τ² = 0.003	-0.32 [-0.85; 0.21] k = 17; τ² = 0.003	-0.00 [-0.73; 0.72] k = 17; τ² = 0.003	-0.13 [-0.45; 0.18] k = 17; τ² = 0.003	**-0.63** **[-1.06; -0.20]** **k = 17; τ² = 0.003**	moderate aerobic	.	.	-0.24 [-0.73; 0.24] k = 1; τ² = NA	0.16 [-0.16; 0.48] k = 1; τ² = NA	0.18 [-0.22; 0.58] k = 1; τ² = NA	.	.
0.46 [-0.30; 1.22] k = 17; τ² = 0.003	0.27 [-0.58; 1.12] k = 17; τ² = 0.003	0.59 [-0.39; 1.57] k = 17; τ² = 0.003	0.46 [-0.23; 1.15] k = 17; τ² = 0.003	-0.04 [-0.84; 0.76] k = 17; τ² = 0.003	0.59 [-0.17; 1.35] k = 17; τ² = 0.003	moderate aerobic + HE	.	.	.	.	.	.
0.12 [-0.44; 0.68] k = 17; τ² = 0.003	-0.07 [-0.74; 0.60] k = 17; τ² = 0.003	0.25 [-0.60; 1.09] k = 17; τ² = 0.003	0.12 [-0.42; 0.66] k = 17; τ² = 0.003	-0.38 [-0.97; 0.20] k = 17; τ² = 0.003	0.25 [-0.30; 0.81] k = 17; τ² = 0.003	-0.34 [-1.22; 0.53] k = 17; τ² = 0.003	moderate aerobic + TAU	.	-0.39 [-1.08; 0.30] k = 1; τ² = NA	.	0.31 [-0.25; 0.86] k = 1; τ² = NA	.
-0.44 **[-0.76; -0.12]** **k = 17; τ² = 0.003**	**-0.63** **[-1.12; -0.14]** **k = 17; τ² = 0.003**	-0.31 [-0.99; 0.37] k = 17; τ² = 0.003	**-0.44** **[-0.65; -0.24]** **k = 17; τ² = 0.003**	**-0.94** **[-1.35; -0.54]** **k = 17; τ² = 0.003**	-0.31 [-0.62; 0.00] k = 17; τ² = 0.003	**-0.90** **[-1.62; -0.18]** **k = 17; τ² = 0.003**	**-0.56** **[-1.11; -0.02]** **k = 17; τ² = 0.003**	passive control	**0.82** **[0.10; 1.54]** **k = 1; τ² = NA**	.	.	.
0.04 [-0.25; 0.33] k = 17; τ² = 0.003	-0.15 [-0.62; 0.33] k = 17; τ² = 0.003	0.17 [-0.52; 0.87] k = 17; τ² = 0.003	0.04 [-0.21; 0.29] k = 17; τ² = 0.003	**-0.46** **[-0.80; -0.12]** **k = 17; τ² = 0.003**	0.17 [-0.11; 0.46] k = 17; τ² = 0.003	-0.42 [-1.15; 0.32] k = 17; τ² = 0.003	-0.08 [-0.55; 0.40] k = 17; τ² = 0.003	**0.48** **[0.22; 0.75]** **k = 17; τ² = 0.003**	TAU	-0.04 [-0.20; 0.27] k = 2; τ² = 0.000	0.09 [-0.28; 0.46] k = 1; τ² = NA	0.64 [-0.04; 1.31] k = 1; τ² = NA
0.06 [-0.23; 0.36] k = 17; τ² = 0.003	-0.13 [-0.63; 0.37] k = 17; τ² = 0.003	0.19 [-0.52; 0.90] k = 17; τ² = 0.003	0.06 [-0.24; 0.36] k = 17; τ² = 0.003	**-0.44** **[-0.84; -0.04]** **k = 17; τ² = 0.003**	0.19 [-0.14; 0.52] k = 17; τ² = 0.003	-0.40 [-1.15; 0.35] k = 17; τ² = 0.003	-0.06 [-0.59; 0.47] k = 17; τ² = 0.003	**0.50** **[0.19; 0.81]** **k = 17; τ² = 0.003**	0.02 [-0.21; 0.24] k = 17; τ² = 0.003	vigorous aerobic	.	.
0.22 [-0.23; 0.67] k = 17; τ² = 0.003	0.03 [-0.55; 0.61] k = 17; τ² = 0.003	0.35 [-0.42; 1.12] k = 17; τ² = 0.003	0.22 [-0.20; 0.64] k = 17; τ² = 0.003	-0.28 [-0.76; 0.20] k = 17; τ² = 0.003	0.35 [-0.09; 0.79] k = 17; τ² = 0.003	-0.24 [-1.05; 0.57] k = 17; τ² = 0.003	0.10 [-0.35; 0.55] k = 17; τ² = 0.003	**0.66** **[0.23; 1.09]** **k = 17; τ² = 0.003**	0.18 [-0.16; 0.52] k = 17; τ² = 0.003	0.16 [-0.25; 0.57] k = 17; τ² = 0.003	vigorous aerobic + TAU	.
0.65 **[0.14; 1.16]** **k = 17; τ² = 0.003**	0.46 [-0.10; 1.02] k = 17; τ² = 0.003	0.78 [-0.03; 1.59] k = 17; τ² = 0.003	**0.65** **[0.11; 1.19]** **k = 17; τ² = 0.003**	0.15 [-0.46; 0.76] k = 17; τ² = 0.003	**0.78** **[0.21; 1.35]** **k = 17; τ² = 0.003**	0.19 [-0.69; 1.07] k = 17; τ² = 0.003	0.53 [-0.17; 1.23] k = 17; τ² = 0.003	**1.09** **[0.55; 1.64]** **k = 17; τ² = 0.003**	**0.61** **[0.10; 1.12]** **k = 17; τ² = 0.003**	**0.59** **[0.06; 1.13]** **k = 17; τ² = 0.003**	0.43 [-0.18; 1.05] k = 17; τ² = 0.003	vigorous strength

Notes: Comparisons are reported in alphabetical order. Estimates are presented as column vs. row for the network meta-analyses (lower diagonal) and row vs. column for the pairwise meta-analyses (upper diagonal) to make network and pairwise meta-analysis results directly comparable. Accordingly, negative values represent superiority of the column-defining treatment in the network evidence (lower diagonal) and of the row-defining treatment in the direct evidence (upper diagonal), respectively; positive values indicate superiority of row-defining treatments in the network evidence and of the column-defining treatment in the direct evidence, respectively. Direct evidence is based on pairwise meta-analysis where k > 1. Effect estimates are presented as standardized mean differences with 95% confidence intervals. Significant results are in bold. K = number of trials per comparison. τ2 = tau-squared. Abbreviations: HE = health education; TAU = treatment as usual.

index: Hedge's g = −0.98, 95% CI: −0.82, −1.15) [88] on sleep quality are small and large, respectively. Therefore, our findings indicate that the effect sizes of aerobic, strength, and mind-body exercises are similar to those of tricyclic antidepressants and trazadone, but smaller than those of CBT-I. However, studies directly comparing hypnotics, CBT-I and exercise are needed for definite conclusions.

Strengths and limitations of the study

The strengths of this review include the comprehensive and updated search, complying with established reporting guidelines, and simultaneously analyzing multiple comparators using network meta-analysis. The latter is especially important since direct evidence is currently lacking. Thus, a comparison of different exercise modes is often only possible through indirect evidence. Furthermore, we did not have to exclude any trials due to language restrictions. Vigorous strength was the only comparator which had significant differences at baseline, and if anything, this difference would lead to smaller effects compared to passive control. There was no evidence for inconsistency. Indirectness and heterogeneity were low for most comparisons. All sensitivity analyses confirmed the treatment estimates. However, our review also has several limitations. We excluded all patients suffering from another significant physical disorder (e.g., cancer), although comorbid depression [89] and insomnia [90] are frequent in these patients. While this decision decreases indirectness, it also limits external validity. The overall risk of bias was high for all trials. Within-study bias was primarily due to a lack of blinding personnel, patients, and outcome assessors. While blinding patients and personnel is impossible in exercise trials, outcome assessors can be blinded. Sample sizes were relatively small in most trials. Confidence in the findings was moderate to very low. This is primarily because outcome assessors were not blinded and methods to avoid selection as well as reporting bias were not clearly described which led to higher risk of within-study bias. Sleep quality data at follow-up and data on important secondary outcomes (e.g. hypnotic use, daytime sleepiness) was insufficient to perform quantitative synthesis.

Future research

There is a large number of trials comparing exercise with other interventions in patients with depression. However, we had to exclude most of these trials because sleep outcomes were not explicitly reported (see Fig. 1 and supplementary file 1 section 4). This lack of evidence is problematic, considering the importance of sleep in onset, treatment trajectory, and relapse-prevention of depression. Future trials should, therefore, include objective (e.g., polysomnography, actigraphy) and subjective (validated questionnaires, e.g., Pittsburgh sleep quality index) sleep outcomes. While the latter are easier to implement, they also increase the risk of detection bias. Despite our extensive literature search in 10 databases (incl. two trial registries) we did not find any trial comparing CBT-I to exercise which reported sleep outcomes. Such a comparison would be an important addition to the literature. Moreover, our analysis shows that secondary outcomes such as adverse events, dropouts, and daytime functioning as well as outcomes at follow-up (i.e., weeks or months after the intervention has ended) are underreported. Future trials should report these outcomes since they are essential to help gauge the benefit-risk ratio.

The neuromuscular and cardiorespiratory challenges posed by aerobic, resistance, and mind-body exercises are very different. Considering that all three exercise types elicited effects may point to potentially different mechanisms of action. These might be primarily of physiological (e.g., production of myokines, thermoregulation, exercise induced BDNF) or *psycho*-physiological (e.g., reduced anxiety, reduced autonomic arousal) nature. Hence, investigating mechanisms of action seems to be a particularly interesting avenue of future investigation. Future studies should compare the additive effects of different exercise modalities to treatment as usual, assess acute and long-term effects, effects of exercise timing during the day, effects of baseline fitness or physical activity, as well as questions of implementation (facilitators and barriers). Although network meta-analyses have many advantages, some of the most pertinent questions of clinical decision making can be best answered with individual patient data meta-analysis. Therefore, trials should make individual patient data available whenever possible. In general, trials should follow established reporting guidelines, especially concerning the implementation and reporting of randomization and allocation procedures, blinding outcome assessors when possible, and using intent-to-treat analysis. Furthermore, exercise trials should register trial protocols to rule out reporting bias. Collectively, these measures will reduce the risk of within-study bias and increase confidence in future evidence.

Implications for clinicians and conclusion

Aerobic, strength, and mind-body exercises are low-cost, non-invasive, and non-pharmacological interventions. The latter is specifically important for most patients who prefer non-pharmacological treatments for depression [91] and insomnia [92]. Moreover, aerobic, strength, and mind-body exercises have an antidepressant effect of a moderate-to-large size, comparable to that of antidepressant medication [40,93–97]. Aerobic exercise also improves quality of life [98] and cardiorespiratory fitness in patients with depression [99]. The latter being especially relevant since it lowers [100] the elevated cardiovascular risk of patients with depression [101,102]. Thus, the findings of our network meta-analysis, which is the first to show that the majority of exercise treatments were similarly effective as treatment as usual, offers the opportunity for individualized treatment choices which may respect patients' individual needs and preferences. This is especially interesting since self-selected exercise intensity seems to elicit the strongest positive affective response in healthy individuals [103]. Lastly, we would like to point out the sensitivity analysis, which was only based on trials that included participants by a formal diagnosis of depression. In this sensitivity analysis, all effect sizes were confirmed, and some effect sizes even substantially increased.

This comprehensive review and network meta-analysis provides evidence that exercise, especially when combined with treatment as usual, improves sleep quality in patients with depression. However, given the risk of bias in individual trials and small sample sizes, the confidence in these findings is moderate to very low. Authors of future trials examining the effect of exercise in patients with depression should, therefore, pay particular attention to methodological rigor, sufficiently large samples, and explicitly reporting sleep outcomes. The latter is especially important considering the pivotal role sleep plays during treatment and in the prevention of relapse of a depressive episode. These results consolidate the current state of evidence, thereby facilitating evidence-based and more personalized choices of patients, health-care professionals, and policy-makers.

Practice points

- The vast majority of exercise types analyzed are significantly superior to passive control in improving sleep quality in depressed patients.
- Mind-body exercise has a statistically significant and clinically relevant additive effect to treatment as usual.
- Implementing mind-body exercise as an add-on treatment seems especially feasible, as it does not require special equipment and relatively little training.

Research agenda

- Trials investigating exercise in patients with depression should include objective and subjective sleep measurements as primary outcomes.
- More research on the mechanisms of action which underlie the effects of exercise on sleep is needed.
- Trials should follow established reporting guidelines, i.e., CONSORT.

Contributors

GB and HG conceived and designed the study. GB and TZS screened the citations, extracted the data, and assessed the risk of bias. GB and HG performed the analysis. GB wrote the first draft of the manuscript. GB, HG, TZS, DS, HP, MG, RvK, and AST contributed to the design as well as revised and approved the final manuscript.

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Ethical approval

Not applicable.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted work; RvK has received personal fees from Vifor AG, Switzerland, outside the submitted work, all other authors have no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

No additional data available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2021.101452.

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Supplementary file 1: Screening

Section 1: Search strings

We built the search string with controlled vocabulary whenever possible and free text. These terms (including appropriate truncation) were selected in an iterative scoping search using the PICOS (patient, intervention, comparator, outcome, study design) approach as well as backward and forward chaining. The study design component was identified using the "Cochrane highly sensitive search strategies for identifying randomized trials" [1] and translated according to the database. Terms within each group were combined with a Boolean "OR" and groups were combined using a Boolean "AND" command.

Reference

[1]Higgins J, Green S, Deeks J, Higgins J, Altman D, editors. Chapter 9: Analysing data and undertaking meta-analyses. Cochrane Handb. Syst. Rev. Interv. Version 510 Updat. March 2011, Available from www.Handbook.Cochrane.Org: The Cochrane Collaboration; 2011.

PubMed

Patient	"Mood Disorders"[Mesh] OR mood disorder*[tw] OR depression*[tw] OR depressive*[tw] OR depressed*[tw] OR affective disorder*[tw] OR dysthym*[tw]
Intervention	"Exercise"[Mesh] OR exercise*[tw] OR exercising[tw] OR "Exercise Therapy"[Mesh] OR "Physical Fitness"[Mesh] OR "Qigong"[Mesh] OR "Tai Ji"[Mesh] OR "Yoga"[Mesh] OR "Resistance Training"[Mesh] OR aerobic activit*[tw] OR physical activit*[tw] OR sport*[tw] OR walk*[tw] OR run*[tw] OR jog*[tw] OR swim*[tw] OR cycling[tw] OR bicycl*[tw] OR physical training*[tw] OR danc*[tw] OR Tai Chi[tw] OR taichi [tw] OR Taiji [tw] OR Tai Ji[tw] OR Tai-Ji[tw] OR Tai Ji[tw] OR Taijiquan[tw] OR T'ai Chi[tw] OR Yoga [tw] OR Qigong [tw] OR Qi-gong [tw] OR qi gong [tw] OR chi gong [tw] OR ch'i kung [tw] OR Baduanjin [tw] OR mind-body exercise [tw] OR meditative movement[tw] OR Resistance[tw] OR pilates[tw] OR strength[tw]
Outcome	"Sleep"[Mesh] OR Sleep*[tw] OR "Sleep Medicine Specialty"[Mesh] OR "Sleep Disorders, Circadian Rhythm"[Mesh] OR "Sleep Initiation and Maintenance Disorders"[Mesh] OR insomnia*[tw]
Study Design	randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh])

EMBASE (on Ovid)

Patient	exp mood disorder/ OR mood disorder$.tw. OR depression$.tw. OR depressive$.tw. OR depressed.tw. OR affective disorder$.tw. OR dysthym$.tw.
Intervention	exp exercise/ OR (exercise$ OR exercising).tw. OR exp kinesiotherapy/ OR exp fitness/ OR aerobic activit$.tw. OR exp physical activity/ OR exp sport/ OR exp Yoga/ OR muscle strength/ OR aerobic activit$.tw. OR physical activit$.tw. OR walk$.tw. OR run$.tw. OR jog$.tw. OR swim$.tw. OR (cycling OR bicycl*).tw. OR physical training$.tw. OR danc$.tw. OR Tai Chi.tw. OR taichi.tw. OR Taiji.tw. OR Tai Ji.tw. OR Tai-Ji.tw. OR Taijiquan.tw. OR Yoga.tw. OR Qigong.tw. OR Qi-gong.tw. OR qi gong.tw. OR chi gong.tw. OR Baduanjin.tw. OR mind-body exercise.tw. OR meditative movement.tw. OR pilates.tw. OR strength.tw.
Outcome	exp sleep/ OR sleep$.tw. OR exp sleep medicine/ OR exp circadian rhythm sleep disorder/ OR exp sleep disorder/ OR insomnia$.tw.
Study Design	(crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random$ or factorial$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.))

Cochrane Library (on cochranelibrary-wiley.com)

Patient	MeSH descriptor: [Mood Disorders] explode all trees OR "mood disorder":ti,ab,kw OR depression*:ti,ab,kw OR depressive*:ti,ab,kw OR depressed:ti,ab,kw OR affective disorder:ti,ab,kw OR dysthym*:ti,ab,kw
Intervention	MeSH descriptor: [Exercise] explode all trees OR (exercise* OR exercising):ti,ab,kw OR MeSH descriptor: [Exercise Therapy] explode all trees OR MeSH descriptor: [Physical Fitness] explode all trees OR MeSH descriptor: [Qigong] explode all trees OR MeSH descriptor: [Tai Ji] explode all trees OR MeSH descriptor: [Yoga] explode all trees OR MeSH descriptor: [Resistance Training] explode all trees OR aerobic activit*:ti,ab,kw OR physical activit*:ti,ab,kw OR sport*:ti,ab,kw OR walk*:ti,ab,kw OR run*:ti,ab,kw OR jog*:ti,ab,kw OR swim*:ti,ab,kw OR (cycling OR bicycl*):ti,ab,kw OR physical training:ti,ab,kw OR danc*:ti,ab,kw OR Tai Chi*:ti,ab,kw OR taichi*:ti,ab,kw OR Taiji*:ti,ab,kw OR Tai Ji*:ti,ab,kw OR Tai-Ji*:ti,ab,kw OR Taijiquan*:ti,ab,kw OR T'ai Chi*:ti,ab,kw OR Yoga*:ti,ab,kw OR Qigong*:ti,ab,kw OR Qi-gong*:ti,ab,kw OR qi gong*:ti,ab,kw OR chi gong*:ti,ab,kw OR ch'i kung*:ti,ab,kw OR Baduanjin*:ti,ab,kw OR mind-body exercise*:ti,ab,kw OR meditative movement*:ti,ab,kw OR Resistance*:ti,ab,kw OR pilates*:ti,ab,kw OR strength*:ti,ab,kw
Outcome	MeSH descriptor: [Sleep] explode all trees OR Sleep*:ti,ab,kw OR MeSH descriptor: [Sleep Medicine Specialty] explode all trees OR MeSH descriptor: [Sleep Disorders, Circadian Rhythm] explode all trees OR MeSH descriptor: [Sleep Initiation and Maintenance Disorders] explode all trees OR insomnia*:ti,ab,kw

Study Design	-

PsycINFO (on Ovid)

Patient	exp MAJOR DEPRESSION/ OR mood disorder*.tw. OR depression$.tw. OR depressive$.tw. OR depressed.tw. OR affective disorder$.tw. OR dysthymia$.tw. OR dysthymic disorder$.tw.
Intervention	exp EXERCISE/ OR (exercise$ OR exercising).tw. OR exp physical fitness/ OR aerobic activit$.tw. OR exp physical activity/ OR exp sports/ OR exp Yoga/ OR exp physical strength/ OR aerobic activit$.tw. OR physical activit$.tw. OR walk$.tw. OR run$.tw. OR jog$.tw. OR swim$.tw. OR (cycling OR bicycl$).tw. OR physical training$.tw. OR exp dance/ OR danc$.tw. OR Tai Chi.tw. OR taichi.tw. OR Taiji.tw. OR Tai-Ji.tw. OR Tai Ji.tw. OR Taijiquan.tw. OR Yoga.tw. OR Qigong.tw. OR Qi-gong.tw. OR qi gong.tw. OR chi gong.tw. OR Baduanjin.tw. OR mind-body exercise.tw. OR meditative movement.tw. OR OR pilates.tw. OR strength.tw.
Outcome	exp SLEEP/ OR sleep$.tw. OR exp sleep treatment/ OR exp sleep disorders/ OR insomnia$.tw.
Study Design	treatment effectiveness evaluation/ or exp Treatment Outcomes/ or placebo/ or exp Followup Studies/ or placebo$.tw. or random$.tw. or comparative stud$.tw. or (clinical adj3 trial$).tw. or (research adj3 design).tw. or (evaluat$ adj3 stud$).tw. or (prospectiv$ adj3 stud$).tw. or ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.

SportDiscus (on EBSCOhost)

Patient	DE "AFFECTIVE disorders" OR DE "MENTAL depression" OR TI "mood disorder*" OR AB "mood disorder*" OR TI depression* OR AB depression* OR TI depressive* OR AB depressive* OR TI depressed OR AB depressed OR TI "affective disorder*" OR AB "affective disorder*" OR TI dysthym* OR AB dysthym*
Intervention	DE "EXERCISE" OR DE "EXERCISE" OR TI (exercise* or exercising) OR AB (exercise* or exercising) OR DE "EXERCISE therapy" OR DE "PHYSICAL fitness" OR TI "aerobic activit*" OR AB "aerobic activit*" OR DE "PHYSICAL activity" OR DE "SPORTS" OR TI walk* OR AB walk* OR TI run* OR AB run* OR TI jog* OR AB jog* OR TI swim* OR AB swim* OR TI (bicycl*) OR AB (bicycl*) OR TI "physical training" OR AB "physical training" OR TI (danc*) OR AB (danc*) OR TI (Tai Chi) OR AB (Tai Chi) OR TI (taichi) OR AB (taichi) OR TI (Taiji) OR AB (Taiji) OR TI (Tai Ji) OR AB (Tai Ji) OR TI (Tai-Ji) OR AB (Tai-Ji) OR TI (Taijiquan) OR AB (Taijiquan) OR TI (T'ai Chi) OR AB (T'ai Chi) OR TI (Yoga) OR AB (Yoga) OR TI (Qigong) OR AB (Qigong) OR TI (Qi-gong) OR AB (Qi-gong) OR TI (qi gong) OR AB (qi gong) OR TI (T'ai Chi) OR AB (T'ai Chi) OR TI (chi gong) OR AB (chi gong) OR TI (ch'i kung) OR AB (ch'i kung) OR TI (Baduanjin) OR AB (Baduanjin) OR TI (mind-body exercise) OR AB (mind-body exercise) OR TI (meditative movement) OR AB (meditative movement) OR DE "PILATES method" OR TI (resistance)

	OR AB (resistance) OR TI (pilates) OR AB (pilates) OR TI (strength) OR AB (strength)
Outcome	DE "SLEEP" OR TI sleep* OR AB sleep* OR DE "SLEEP disorders" OR DE "SLEEP interruptions" OR TI insomnia* OR AB insomnia*
Study Design	PT Clinical trial OR AB random* OR TI random* OR AB placebo or TI placebo OR SU drug therapy OR AB trial OR TI trial OR AB groups or TI groups NOT (SU animals NOT human)

CINHAL (on EBSCOhost)

Patient	(MH "Affective Disorders+") OR TI (mood disorder*) OR AB (mood disorder*) OR TI depression* OR AB depression* OR TI depressive* OR AB depressive* OR TI depressed OR AB depressed OR TI (affective disorder*) OR AB (affective disorder*) OR TI dysthym* OR AB dysthym*
Intervention	(MH "Exercise+") OR TI (exercise* or exercising) OR AB (exercise* or exercising) OR (MH "Therapeutic Exercise") OR (MH "Physical Fitness") OR (MH "Qigong") OR (MM "Tai Chi") OR (MM "Yoga") OR (MH "Muscle Strengthening+") OR TI (aerobic activit*) OR AB (aerobic activit*) OR (MH "Physical Activity") OR (MH "Sports+") OR AB walk* OR TI walk* OR AB run* OR TI run* OR AB jog* OR TI jog* OR AB swim* OR TI swim* OR TI bicycl* OR AB bicycl* OR TI (physical training) OR AB (physical training) OR TI danc* OR AB danc* OR TI Tai Chi OR AB Tai Chi OR TI taichi OR AB taichi OR TI Taiji OR AB Taiji OR TI Tai Ji OR AB Tai Ji OR TI Tai-Ji OR AB Tai-Ji OR TI Taijiquan OR AB Taijiquan OR TI T'ai Chi OR AB T'ai Chi OR TI Yoga OR AB Yoga OR TI Qigong OR AB Qigong OR TI Qi-gong OR AB Qi-gong OR TI qi gong OR AB qi gong OR TI chi gong OR AB chi gong OR TI ch'i kung OR AB ch'i kung OR TI Baduanjin OR AB Baduanjin OR TI mind-body exercise OR AB mind-body exercise OR TI meditative movement OR AB meditative movement OR TI Resistance OR AB Resistance OR TI pilates OR AB pilates OR TI strength OR AB strength
Outcome	(MH "Sleep") OR TI sleep* OR AB sleep* OR (MH "Sleep Disorders, Circadian Rhythm") OR (MH "Sleep Disorders") OR (MH "Insomnia") OR TI (insomnia*) OR AB (insomnia*)
Study Design	PT Clinical trial OR AB random* OR TI random* OR AB placebo or TI placebo OR SU drug therapy OR AB trial OR TI trial OR AB groups or TI groups NOT (SU animals NOT human)

OpenGrey (on opengrey.eu)

Patient	("mood disorder*" OR depression* OR depressive* OR depressed OR "affective disorder*" OR dysthym*)
Intervention	(exercise* OR exercising OR "aerobic activit*" OR "physical activit*" OR sport* OR walk* OR run* OR jog* OR swim* OR cycling OR bicycl* OR "physical training*" OR danc* OR pilates OR "Tai Chi" OR "taichi" OR "Taiji" OR "Tai Ji" OR "Tai-Ji" OR "Taijiquan" OR "T'ai Chi" OR

	"Yoga" OR "Qigong" OR "Qi-gong" OR "qi gong" OR "chi gong" OR "ch'i kung" OR "Baduanjin" OR "mind-body exercise" OR "meditative movement" OR Resistance OR strength)
Outcome	(Sleep* OR insomnia*))
Study Design	-

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Patient	(SU(mental depression) OR ti("mood disorder*" OR depression* OR depressive* OR depressed OR "affective disorder*" OR dysthym*) OR ab("mood disorder*" OR depression* OR depressive* OR depressed OR "affective disorder*" OR dysthym*))
Intervention	(SU(exercise OR physical fitness) OR SU(yoga) OR ti(exercise* OR exercising OR "aerobic activit*" OR "physical activit*" OR sport* OR walk* OR run* OR jog* OR swim* OR cycling OR bicycl* OR "physical training*" OR danc* OR pilates OR Tai Chi OR taichi OR Taiji OR Tai Ji OR Tai-Ji OR Taijiquan OR T'ai Chi OR Yoga OR Qigong OR Qi-gong OR qi gong OR chi gong OR Baduanjin OR mind-body exercise OR meditative movement OR Resistance OR strength) OR ab(exercise* OR exercising OR "aerobic activit*" OR "physical activit*" OR sport* OR walk* OR run* OR jog* OR swim* OR cycling OR bicycl* OR "physical training*" OR danc* OR pilates OR Tai Chi OR taichi OR Taiji OR Tai Ji OR Tai-Ji OR Taijiquan OR T'ai Chi OR Yoga OR Qigong OR Qi-gong OR qi gong OR chi gong OR Baduanjin OR mind-body exercise OR meditative movement OR Resistance OR strength))
Outcome	(SU(sleep) OR SU(sleep disorder) OR SU(insomnia) OR ti(Sleep* OR insomnia*) OR ab(sleep* OR insomnia*))
Study Design	-

Clinicaltrials.gov

Patient	Mood disorder OR affective disorder OR depression OR depressive OR depressed OR dysthym*
Intervention	Exercise OR exercising OR physical activity OR aerobic activity OR sport OR walking OR jogging OR swimming OR bicycle OR cycling OR physical training OR dancing OR mind-body OR meditative movement OR qi gong OR tai chi OR yoga OR resistance OR strength OR pilates
Outcome	Sleep OR Circadian Rhythm OR insomnia
Study Design	Interventional Studies

WHO International Clinical Trials Registry

Condition	Mood disorder OR affective disorder OR depression OR depressive OR depressed OR dysthym*

Intervention	Exercise OR exercising OR physical activity OR aerobic activity OR sport OR walking OR running OR jogging OR swimming OR bicycle OR cycling OR dancing OR mind-body OR meditative movement OR qi gong OR tai chi OR yoga OR resistance OR pilates OR strength
Outcome	-
Study Design	-

Section 2: Contacted authors and their replies

Concerning trial	Request	Reply
Abedi, P., Nikkhah, P., & Najar, S. (2015). Effect of pedometer-based walking on depression, anxiety and insomnia among postmenopausal women. Climacteric, 18(6), 841-845.	Mean and SD of sleep outcome at baseline and post-intervention	no reply
Singh, N. A., Stavrinos, T. M., Scarbek, Y., Galambos, G., Liber, C., Fiatarone Singh, M. A., & Morley, J. E. (2005). A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. The Journals of Gerontology: Series A, 60(6), 768-776.	Mean and SD of sleep outcome at baseline and post-intervention	no reply
Combs, K., Smith, P. J., Sherwood, A., Hoffman, B., Carney, R. M., Freedland, K., ... & Blumenthal, J. A. (2014). Impact of sleep complaints and depression outcomes among participants in the standard medical intervention and long-term exercise study of exercise and pharmacotherapy for depression. The Journal of nervous and mental disease, 202(2), 167-171.	Mean and SD of sleep outcome at baseline and post-intervention	Information was provided
Rethorst, C. D., Sunderajan, P., Greer, T. L., Grannemann, B. D., Nakonezny, P. A., Carmody, T. J., & Trivedi, M. H. (2013). Does exercise improve self-reported sleep quality in non-remitted major depressive disorder?. Psychological medicine, 43(4), 699-709.	Mean and SD of sleep outcome at baseline and post-intervention	no reply
Pinniger, R., Thorsteinsson, E. B., Brown, R. F., & McKinley, P. (2013). Tango dance can reduce distress and insomnia in people with self-referred affective symptoms. American Journal of Dance Therapy, 35(1), 60-77.	Mean and SD of sleep outcome at baseline and post-intervention	Information was provided
Dritsa, M., Dupuis, G., Lowensteyn, I., & Da Costa, D. (2009). Effects of home-based exercise on fatigue in postpartum depressed women: who is more likely to benefit and why?. Journal of psychosomatic research, 67(2), 159-163.	Mean and SD of sleep outcome at baseline and post-intervention	Information was provided
Gerber, M., Minghetti, A., Beck, J., Zahner, L., & Donath, L. (2019). Is improved fitness following a 12-week exercise program associated with decreased symptom severity, better wellbeing, and fewer sleep complaints in patients with major depressive disorders? A secondary analysis of a randomized controlled trial. Journal of psychiatric research, 113, 58-64.	Mean and SD of sleep outcome at baseline and post-intervention	Information was provided
Strid, C., Andersson, C., Forsell, Y., Öjehagen, A., & Lundh, L. G. (2016). Internet-based cognitive behaviour therapy and physical exercise–Effects studied by automated telephone assessments in mental ill-health patients; a	Mean and SD of sleep outcome at baseline and	Information was provided

randomized controlled trial. British Journal of Clinical Psychology, 55(4), 414-428.	post-intervention	
Arrant, K. R. (2019). The Effect of a Yoga Intervention on Sleep and Stress (Doctoral dissertation, The University of Mississippi Medical Center).	Mean and SD of sleep outcome at baseline and post-intervention	no reply
Protocol-ID: NCT02260843	Is data available?	no reply
Protocol-ID: NCT01383811	Is data available?	no reply
Protocol-ID: NCT03191994	Is data available?	no reply
Protocol-ID: ACTRN12618001453279	Is data available?	data not yet published
Protocol-ID: NCT02907476	Is data available?	no reply
Protocol-ID: NCT03720145	Is data available?	data not yet published
Protocol-ID: IRCT20180506039542N1	Is data available?	no reply
Protocol-ID: IRCT2016111630924N1	Is data available?	no reply
Protocol-ID: NTR3460	Is data available?	data not yet published
Protocol-ID: NTR4168	Is data available?	trial was stopped, no outcomes are available

ChiCTR = Chinese Clinical Trial Registry; NCT = National Clinical Trial (clinicaltrials.gov); ACTRN = Australian New Zealand Clinical Trials Registry; IRCT = Iranian Registry of Clinical Trials; NTR = Netherlands Trial Register

Section 3:
Number of excluded papers at full text level due to language constraints: 0

Section 4: References excluded at full text screening and the reasons therefore

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Section 5: Number of disagreements at each level of screening

Screening level	N disagreements	N disagreements resolved by discussion	N disagreements resolved by arbitration	N screened
Title & abstract	230	230	0	7725
Full text	10	10	0	337

Supplementary file 2: Analysis and results

Section 1: Indirectness table with patient and intervention characteristics per node

Node	Trial	Mean age in each trial arm (years)	Female	baseline depression	intervention	duration (weeks)	total number of sessions	length of individual sessions (minutes)	number of sessions / week	total exposure to intevention (min)	Outcome	Head to head comparissons between	Population indirectness	Intervention indirectness	Outcome indirectness	Comparisons indirectness	Total indirectness
TAU*	Strid et al. 2016	43	73%	moderate	internet-CBT	12	12	-	1	-	Karolinska Sleep Questionnaire	TAU, mind-body exercise, moderate aerobic exercise, vigorous aerobic exercise	low	low	low	low	low
TAU*	Strid et al. 2016	43	73%	moderate	general practitioner care	12	-	-	-	-	Karolinska Sleep Questionnaire	TAU, mind-body exercise, moderate aerobic exercise, vigorous aerobic exercise	low	low	low	low	low
TAU	Lavretsky et al. 2011	71	62%	subthreshold (after run-in with antidepressant)	health education + SSRI	10	10	120	1	1200	PSQI	mind-body exercise + TAU, TAU	high	low	low	low	high
TAU	Chan et al. 2012	46	80%	moderate	CBT + antidepressant	10	10	90	1	900	sleep-related items of HAMD	mind-body exercise + TAU, TAU, passive control	low	low	low	low	low
TAU	Cheung et al. 2018	48	79%	moderate	treatment as usual	12	-	-	-	-	PSQI	moderate aerobic exercise + TAU, TAU	low	low	low	low	low
TAU	Rethorst et al. 2013	47	82%	moderate	4 KKW + SSRI	12	-	-	minimum 1 / week	-	sleep related items of IDS-C	vigorous aerobic exercise + TAU, TAU	moderate or unclear	low	low	low	low
TAU	Köhn et al. 2013	53	92%	mild	treatment as usual	12	-	-	-	-	ISI	mind-body exercise + TAU, TAU	moderate or unclear	low	low	low	low
TAU	Singh et al. 2005	69	55%	moderate	general practitioner care	8	-	-	-	-	PSQI	high intensity strength exercise, low intensity strength exercise, TAU	high	low	low	low	high
TAU	Combs et al. 2014	52	76%	moderate	sertraline therapy	16	6	0	0	0	sleep-related items of HAMD	vigorous aerobic exercise, vigorous aerobic exercise, TAU, active control (not TAU)	low	low	low	low	low
		mean: 52	mean: 75%	subthreshold = 1; mild = 1; moderate = 7; severe = 0		mean: 11.6	mean: 9.5	mean: 70	mean: 0.8	mean: 700	PSQI or ISI = 4; other self-reported questionnaires = 2; clinicial rated sleep-quality = 3						
active control (not TAU)	Singh et al. 1997	71	59%	mild	health education	10	20	60	2	1200	PSQI	high intensity strength exercise, active control (not TAU)	high	low	low	low	high
active control (not TAU)	Afonso et al. 2012	Range: 50-65	100%	mild	passive stretching	16	32	60	2	1920	ISI	passive control, mind-body exercise, active control (not TAU)	moderate or unclear	low	low	low	low
active control (not TAU)	Combs et al. 2014	52	76%	moderate	placebo pill	16	-	-	-	-	sleep-related items of HAMD	vigorous aerobic exercise, vigorous aerobic exercise, TAU, active control (not TAU)	low	low	low	low	low
active control (not TAU)	Pinniger et al. 2013	40	89%	mild	tango dance	8	8	60	1	480	ISI	low intensity strength exercise, passive control, meditation, active control (not TAU)	moderate or unclear	low	low	low	low
		mean: 54	mean: 81%	mild = 3; moderate = 1; severe = 0		mean: 12.5	mean: 20	mean: 60	mean: 1.7	mean: 1200	PSQI or ISI = 3; other self-reported questionnaires = 0; clinicial rated sleep-quality = 1						

Node	Trial	Mean age in each trial arm (years)	Female	baseline depression	intervention	duration (weeks)	total number of sessions	length of individual sessions (minutes)	number of sessions / week	total exposure to intevention (min)	Outcome	Head to head comparissons between	Population indirectness	Intervention indirectness	Outcome indirectness	Comparisons indirectness	Total indirectness
passive control	Afonso et al. 2012	Range: 50-65	100%	mild	no treatment control	16	-	-	-	-	ISI	passive control, mind-body exercise, active control (not TAU)	moderate or unclear	low	low	low	low
passive control	Oretzky et al. 2007	26	76%	moderate	wait-list control	5	-	-	-	-	PSQI	mind-body exercise, passive control	low	low	low	low	low
passive control	Pinniger et al. 2013	40	89%	mild	wait-list control	8	-	-	-	-	ISI	low intensity strength exercise, passive control, meditation, active control (not TAU)	moderate or unclear	low	low	low	low
passive control	Dritsa et al. 2009	34	100%	EPDS: mean = 13.7, SD = 3.9	no treatment control	12	-	-	-	-	PSQI	moderate aerobic exercise, passive control	moderate or unclear	low	low	low	low
passive control	Field et al. 2013	27	100%	CES-D: mean = 29.5, SD = 10.7	wait-list control	12	-	-	-	-	Snyder-Halpern and Verran scale	mind-body exercise, passive control	moderate or unclear	low	low	low	low
passive control	Chan et al. 2016	55	75%	CES-D: mean = 21.2, SD = 6.56	wait-list control	8	-	-	-	-	PSQI	mind-body exercise, passive control	moderate or unclear	low	low	low	low
passive control	Chan et al. 2012	46	80%	moderate	wait-list	10	-	-	-	-	sleep-related items of HAMD	mind-body exercise + TAU, TAU, passive control	low	low	low	low	low
		mean: 38	mean: 89%	mild = 2; moderate = 2; severe = 0		mean: 10.1					PSQI or ISI = 5; other self-reported questionnaires = 1; clinicial rated sleep-quality = 1						
mind-body exercise	Oretzky et al. 2007	26	76%	moderate	yoga	5	10	60	2	600	PSQI	mind-body exercise, passive control	low	low	low	low	low
mind-body exercise	Schuver et al. 2014	43	100%	moderate	mindfulnes-based yoga	12	24	60	2	1440	PSQI	mind-body exercise, other	moderate or unclear	low	low	low	low
mind-body exercise	Field et al. 2013	27	100%	CES-D: mean = 29.5, SD = 10.7	tai chi / yoga	12	12	20	1	240	Snyder-Halpern and Verran scale	mind-body exercise, passive control	moderate or unclear	low	low	low	low
mind-body exercise	Chan et al. 2016	55	75%	CES-D: mean = 21.2, SD = 6.56	integrative body-mind-spirit	8	8	180	1	1440	PSQI	mind-body exercise, passive control	moderate or unclear	low	low	low	low
mind-body exercise	Afonso et al. 2012	Range: 50-65	100%	mild	yoga	16	32	60	2	1920	ISI	passive control, mind-body exercise, active control (not TAU)	moderate or unclear	low	low	low	low
mind-body exercise	Strid et al. 2016	43	73%	moderate	yoga	12	36	60	3	2160	Karolinska Sleep Questionnaire	TAU, TAU, mind-body exercise, moderate aerobic exercise, vigorous aerobic exercise	low	low	low	low	low
		mean: 39	mean: 87%	mild = 1; moderate = 3; severe = 0		mean: 10.8	mean: 20.3	mean: 73.3	mean: 1.8	mean: 1300	PSQI or ISI = 4; other self-reported questionnaires = 2; clinicial rated sleep-quality = 0						
mind-body exercise + TAU	Lavretsky et al. 2011	71	62%	subthreshold (after run-in with antidepressant)	Tai Chi Chih + SSRI	10	10	120	1	1200	PSQI	mind-body exercise + TAU, TAU	high	low	low	low	high
mind-body exercise + TAU	Chan et al. 2012	46	80%	moderate	Dejian Mind-Body Intervention + antidepressant	10	10	90	1	900	sleep-related items of HAMD	mind-body exercise + TAU, TAU, passive control	low	low	low	low	low
mind-body exercise + TAU	Köhn et al. 2013	53	92%	mild	yoga + TAU	12	12	60	1	720	ISI	mind-body exercise + TAU, TAU	moderate or unclear	low	low	low	low
		mean: 57	mean: 78%	subthreshold = 1; mild = 1; moderate = 1; severe = 0		mean: 11	mean: 11	mean: 90	mean: 1	mean: 940	PSQI or ISI = 2; other self-reported questionnaires = 0; clinicial rated sleep-quality = 1						

Node	Trial	Mean age in each trial arm (years)	Female	baseline depression	intervention	duration (weeks)	total number of sessions	length of individual sessions (minutes)	number of sessions / week	total exposure to intevention (min)	Outcome	Head to head comparissons between	Population indirectness	Intervention indirectness	Outcome indirectness	Comparisons indirectness	Total indirectness
light intensity strength exercise	Pinniger et al. 2013	40	89%	mild	circuit exercise	8	8	60	1	480	ISI	low intensity strength exercise, passive control, meditation, active control (not TAU)	moderate or unclear	low	low	low	low
light intensity strength exercise	Singh et al. 2005	69	55%	moderate	low intensity resistance training	8	24	60	3	1440	PSQI	high intensity strength exercise, low intensity strength exercise, TAU	high	low	low	low	high
		mean: 54	mean: 72%	mild = 1; moderate = 1; severe = 0		mean: 8	mean: 16	mean: 60	mean: 2	mean: 960	PSQI or ISI = 2; other self-reported questionnaires = 0; clinicial rated sleep-quality = 0						
vigorous intensity strength exercise	Singh et al. 2005	69	55%	moderate	high-intensity progressive resistance training	8	24	60	3	1440	PSQI	high intensity strength exercise, low intensity strength exercise, TAU	high	low	low	low	high
vigorous intensity strength exercise	Singh et al. 1997	71	59%	mild	high-intensity progressive resistance training	10	30	60	3	1800	PSQI	high intensity strength exercise, active control (not TAU)	high	low	low	low	high
		mean: 70	mean: 57%	mild = 1; moderate = 1; severe = 0		mean: 9	mean: 27	mean: 60	mean: 3	mean: 1620	PSQI or ISI = 2; other self-reported questionnaires = 0; clinicial rated sleep-quality = 0						
moderate aerobic exercise	Dritsa et al. 2009	34	100%	EPDS: mean = 13.7, SD = 3.9	moderate aerobic exercise	12	-	60-120min / week	-	720-1440min	PSQI	moderate aerobic exercise, passive control	moderate or unclear	low	low	low	low
moderate aerobic exercise	Strid et al. 2016	43	73%	moderate	moderate aerobic exercise	12	36	60	3	2160	Karolinska Sleep Questionnaire	TAU, TAU, mind-body exercise, moderate aerobic exercise, vigorous aerobic exercise	low	low	low	low	low
		mean: 38	mean: 87%	mild = 0; moderate = 1; severe = 0		mean: 12	mean: 36	mean: 60	mean: 3	mean = 1620	PSQI or ISI = 1; other self-reported questionnaires = 1; clinicial rated sleep-quality = 0						
moderate aerobic exercise + TAU	Cheung et al. 2018	48	79%	moderate	moderate aerobic exercise + TAU	12	36	30	3	1080	PSQI	moderate aerobic exercise + TAU, TAU	low	low	low	low	low
moderate aerobic exercise + TAU	Gerber et al. 2019	36	77%	severe	moderate aerobic exercise training + inpatient TAU	4	12	35	3	420	ISI	moderate aerobic exercise + TAU, vigorous aerobic exercise + TAU	high	low	low	low	high
		mean: 42	mean: 78%	mild = 0; moderate = 1; severe = 1		mean: 8	mean: 24	mean: 33	mean: 3	mean: 750	PSQI or ISI = 2; other self-reported questionnaires = 0; clinicial rated sleep-quality = 0						
vigorous aerobic exercise*	Combs et al. 2014	52	76%	moderate	vigorous supervised exercise	16	48	45	3	2160	sleep-related items of HAMD	vigorous aerobic exercise, TAU, active control (not TAU)	low	low	low	low	low
vigorous aerobic exercise*	Combs et al. 2014	52	76%	moderate	vigorous home-based exercise	16	48	45	3	2160	sleep-related items of HAMD	vigorous aerobic exercise, TAU, active control (not TAU)	low	low	low	low	low
vigorous aerobic exercise	Strid et al. 2016	43	73%	moderate	vigorous aerobic exercise	12	36	60	3	2160	Karolinska Sleep Questionnaire	TAU, TAU, mind-body exercise, moderate aerobic exercise, vigorous aerobic exercise	low	low	low	low	low
		mean: 49	mean: 75%	mild = 0; moderate = 3; severe = 0		mean: 15	mean: 44	mean: 50	mean: 3	mean: 2160	PSQI or ISI = 0; other self-reported questionnaires = 1; clinicial rated sleep-quality = 2						

Node	Trial	Mean age in each trial arm (years)	Female	baseline depression	intervention	duration (weeks)	total number of sessions	length of individual sessions (minutes)	number of sessions / week	total exposure to intevention (min)	Outcome	Head to head comparissons between	Population indirectness	Intervention indirectness	Outcome indirectness	Comparisons indirectness	Total indirectness
vigorous aerobic exercise + TAU	Rethorst et al. 2013	47	82%	moderate	16 KKW + SSRI	12	-	-	minimum 1 / week	-	sleep related items of IDS-C	vigorous aerobic exercise + TAU, TAU	moderate or unclear	low	low	low	low
vigorous aerobic exercise + TAU	Gerber et al. 2019	36	77%	severe	sprint interval training + inpatient TAU	4	12	35	3	420	ISI	moderate aerobic exercise + TAU, vigorous aerobic exercise + TAU	high	low	low	low	high
		mean: 42	mean: 80%	mild = 0; moderate = 1; severe = 1		mean: 8	mean: 12	mean: 35	mean: 3	mean: 420	PSQI or ISI = 1; other self-reported questionnaires = 0; clinicial rated sleep-quality = 1						
meditation	Pinniger et al. 2013	40	89%	mild	meditation	8	8	60	1	480	ISI	low intensity strength exercise, passive control, meditation, active control (not TAU)	moderate or unclear	low	low	low	low
moderate aerobic + health education	Schuver et al. 2014	43	100%	moderate	moderate walking + health education	12	24	60	2	1440	PSQI	mind-body exercise, other	moderate or unclear	low	low	low	low

Note: * These study arms were each combined into one arm within the trials Strid 2016 and Combs 2014 before entering into the network meta-analysis, see also Section 2 Data preprocessing
Abbreviations: TAU = treatment as usual; CBT = cognitive behavioral treatment; SSRI = selective serotonin reuptake inhibitor; KKW = kilocalories per kilogram body weight per week; PSQI = Pittsburgh Sleep Quality Index; EPDS = Edinburgh Postnatal Depression Scale; CES-D = Center for Epidemiologic Studies Depression Scale; HAMD = Hamilton Rating Scale for Depression; IDS-C = Inventory of Depressive Symptomatology Clinician Version; ISI = Insomnia Severity Index;

PSQI and ISI are highly correlated [1] and do not differ in terms of diagnostic properties [2].

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Section 2:
2a: Data preprocessing

The data of some trials had to be preprocessed to enable quantitative analyses.

Singh et al. 2005 [1] only reported mean and standard deviations of change scores from baseline to post-intervention. Since the authors could not provide the means and standard deviations at post-intervention, we calculated standardized mean differences from the standardized mean change scores.

Combs et al. 2014 [2] allocated patients to one of four interventions: 1) supervised exercise, 2) home-based exercise, 3) sertraline therapy or 4) placebo. The intervention modalities of the exercise arms were identical except for the supervision, i.e. supervised vs. home-based. We decided to combine these two exercise arms, since there were no baseline differences, both treatment arms had similar effect sizes when compared to the placebo group, and combining them would yield a larger power in the network meta-analysis.

Strid et al. 2016 [3] allocated patients to one of five interventions: 1) treatment as usual by physician, 2) internet cognitive behavioral therapy, 3) low-intense training (yoga), 4) moderate aerobic exercise or 5) vigorous aerobic exercise. We combined the first two groups and classified them as treatment as usual. Our rationale for this was that in this trial 'treatment as usual' consisted mostly of counselling with a cognitive behavioral focus and cognitive behavioral therapy is recommended by treatment guidelines for depression [4].

Cheung & Lee 2017 [5] only reported median and interquartile ranges. We transformed these values into means and standard deviations according to the method of Wan et al. 2014 [6] which has been shown to be one of the most unbiased formulas for these cases [7].

Rethorst et al. 2013 [8] only reported the outcome of interest in a graphical output of an adjusted analysis. Since the authors did not reply to our inquiry, we extracted the data using the software DigitizeIt [9]. We used the largest standard deviation reported for this outcome at baseline for both groups at follow-up.

We performed sensitivity analyses by excluding each of these trials individually and comparing the effects to the original results, see section 9.

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2b: Network meta-analysis details

The magnitude of SMD was interpreted as small (0.20), moderate (0.50), or large (0.80) [1].

Indirect evidence was estimated using the entire network of evidence within a frequentist framework. Random-effects *netmeta* [2] accounts for dependencies between comparisons in the case of multi-arm trials [3]. The command *pairwise* was used in the case of multi-arm trials, to transform the dataset to the comparison level, which is needed for conducting the network meta-analysis.

The Q statistic was used to calculate statistical heterogeneity between studies on the pairwise level [4]. Further τ^2 was analyzed to estimate the variance caused by the distribution of the true study means [5]. I^2 was evaluated to indicate the amount of observed variance that can be attributed to between-study heterogeneity [6]. In network meta-analysis, we assumed a common estimate for the heterogeneity variance across the different comparisons. We assumed that any patient who met all inclusion criteria was likely, in principle, to be randomized to any of the interventions in the synthesis comparator set. We addressed the assumption of transitivity [7] in the network meta-analysis by first assessing whether the included interventions were similar across studies using a different design, and then checking whether the distribution of potential moderators was balanced across comparisons [8]. We assumed 2-sided $p < .05$ to indicate statistical significance for all conducted analyses.

Local and global methods were used to detect inconsistency [9], using the netsplit and decomp functions of *netmeta* [2]. The presence of inconsistency was evaluated using the following approaches: (1) locally using the *netsplit* command (i.e., testing the difference between estimates derived from direct evidence and estimates derived from indirect evidence for statistical significance) and (2) globally using the *decomp.design* command (i.e., using the design-by-treatment interaction model). We compared the magnitude of heterogeneity between consistency and inconsistency models to determine how much heterogeneity was explained by inconsistency.

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Section 3: Sources of funding

Trial	Funding
Lavretsky 2011	academic grants
Rethorst 2013	academic grants
Dritsa 2009	academic grants
Köhn 2013	academic grants
Singh 1997	academic grants
Afonso 2012	academic grants
Chan 2012	mix of public and other funds
Field 2013	mix of public and other funds
Singh 2005	funding not specified
Combs 2014	funding not specified
Oretzky 2007	funding not specified
Cheung 2018	funding not specified
Schuver 2014	funding not specified
Pinniger 2013	funding not specified
Gerber 2019	funding not specified
Strid 2016	funding not specified
Chan 2016	funding not specified

Section 4: Baseline characteristics and intervention modalities of trials included in the network meta-analysis

First author (year)	N	Age (mean)	Average baseline depression severity	Concomitant therapy	Outcome measure	Duration of intervention (weeks)	Intervention type	Intensity	Intervention frequency and duration	Adherence	Clinical setting / in- vs. outdoor / individual vs. group / supervision
Afonso et al. 2012 [1]	44	not reported, range: 50-65	mild	no	ISI	16	wait-list	-	-	-	- / - / - / -
							yoga	light	2x 60min / week	not reported	outpatient / indoor / group / supervised
Chan et al. 2012 [2]	50	46.5	moderate	antidepressants & unspecified number of meetings with psychiatrists	sleep-related items on HAMD-17	10	waitlist	-	-	-	- / - / - / -
							Cogntitive behavioral therapy	-	1x 90min / week	minimum 70%	outpatient / indoor / group / supervised
							Dejian Mind-Body Intervention	light	1x 90min / week	minimum 70%	outpatient / not reported / group / supervised
Chan et al. 2017 [3]	185	55.3	CES-D, mean=21.2 (SD=6.56)	no information	PSQI	8	wait-list	-	-	-	- / - / - / -
							I-BMS	light	1x 180min / week	not reported	outpatient / not reported / group / supervised
Cheung et al. 2018 [4]	34	47.8	moderate	usual care (pharmacotherapy, psychological treatment)	PSQI	12	no additional treatment	-	not specified	-	- / - / - / -
							aerobic exercise	moderate	3x 30min / week	not reported	outpatient / not reported / mixed / mixed
Combs et al. 2014‡ [5]	202	51.7	moderate	no	sleep-related items on HAMD-17	16	placebo	identical to sertraline group	6 meetings with study psychiatrist	not reported	outpatient / - / - / -
							sertraline therapy	50-200mg, titriation depending on response	6 meetings with study psychiatrist	not reported	outpatient / - / - / -
							home-based exercise	vigorous	3x 45min / week	not reported	at home / not reported / not reported / none
							supervised exercise	vigorous	3x 45min / week	not reported	outpatient / indoor / not reported / supervised
Dritsa et al. 2009‡ [6]	88	33.6	EPDS, mean=13.7 (SD=3.9)	no	PSQI	12	no treatment	-	-	-	- / - / - / -
							exercise	mixed	60min / week (unspecified frequency)	76%	mixed / not reported / not reported / mixed
Field et al. 2013 [7]	92	26.6	CES-D, mean=29.5 (SD=10.7)	no	VSH	12	waitlist control group	-	NA	-	- / - / - / -
							Tai chi/yoga	light	1x 20min / week	not reported	outpatient / not reported / group / supervised
Gerber et al. 2019‡ [8]	53	36.3	severe	inpatient usual care (pharmacotherapy, psychological treatment)	ISI	4	Continuous aerobic exercise training	moderate	3x 35min / week	minimum 92%	inpatient / indoor / individually / supervised
							Sprint interval training	vigorous	3x 35min / week	minimum 92%	inpatient / indoor / individually / supervised

First author (year)	N	Age (mean)	Average baseline depression severity	Concomitant therapy	Outcome measure	Duration of intervention (weeks)	Intervention type	Intensity	Intervention frequency and duration	Adherence	Clinical setting / in- vs. outdoor / individual vs. group / supervision
Köhn et al. 2013 [9]	37	53	mild	usual care (pharmacotherapy, psychological treatment)	ISI	12	no additional treatment	-	-	-	- / - / - / -
							yoga group	light	1x 60min / week	96%	outpatient / not reported / group / supervised
Lavretsky et al. 2011 [10]	73	70.5	subthreshold (after run-in with antidepressant)	10-20mg escitalopram / day	PSQI	10	health education (matching duration, frequency & social contact)	light	1x 120min / week	not reported	not reported / not reported / group / supervised
							Tai Chi Chih	light	1x 120min / week	not reported	not reported / not reported / group / supervised
Oretzky et al. 2006 [a] [11]	58	25.6	moderate	no	PSQI	5	waitlist	-	NA	-	- / - / - / -
							yoga	light	2x 60min / week	90%	outpatient / indoor / group / supervised
Pinniger et al. 2013† [12]	49	39.5	mild	no information	ISI	8	waitlist	-	-	-	- / - / - / -
							meditation	-	1x 60min / week	not reported	outpatient / not reported / group / supervised
							tango dance	light	1x 60min / week	not reported	outpatient / not reported / group / supervised
							resistance exercise	light	1x 60min / week	not reported	outpatient / not reported / group / supervised
Rethorst et al. 2013+ [13]	122	47	moderate	SSRI	sleep-related itmes of IDS-C	12	low-dose (4kcal/week/kilogram body weight) exercise augmentation	mixed	minimum 1/week (unspecified frequency)	99%	mixed / mixed / not reported / mixed
							public health dose (16kcal/week/kilogram body weight) exercise augmentation	mixed	minimum 1/week (unspecified frequency)	64%	mixed / mixed / not reported / mixed
Schuver et al. 2014 [a] [14]	40	42.7	moderate	mixed	PSQI	12	mindfulness-based yoga	light	2x 60min / week	100%	at home / indoor / individually / mixed
							walking health education	moderate	2x 60min / week	65%	at home / indoor / individually / mixed
Singh et al. 1997 [15]	32	71.3	mild	mixed	PSQI	10	health education	-	2x 60min / week	95%	outpatient / indoor / group / supervised
							exercise	vigorous	3x 60min / week	93%	outpatient / indoor / mixed / supervised
Singh et al. 2005 [16]	60	69.3	moderate	no	PSQI	8	usual care (no restrictions) from general practitioner	-	-	-	- / - / - / -
							progressive resistance training	light	3x 60min / week	99%	outpatient / indoor / mixed / supervised
							progressive resistance training	vigorous	3x 60min / week	95%	outpatient / indoor / mixed / supervised

First author (year)	N	Age (mean)	Average baseline depression severity	Concomitant therapy	Outcome measure	Duration of intervention (weeks)	Intervention type	Intensity	Intervention frequency and duration	Adherence	Clinical setting / in- vs. outdoor / individual vs. group / supervision
Strid et al. 2016‡ [17]	879	42.8	moderate	no information	KSQ	12	treatment as usual by physician	-	-	-	- / - / - / -
							internet cognitive behavioral therapy	not exercise intervention	1module / week (on average 16min)	65% (mean = 7.8 completed modules)	at home / not reported / individually / supervised
							yoga	light	3x 60min / week	28%	outpatient / indoor / group / supervised
							aerobic exercise	moderate	3x 60min / week	23%	outpatient / indoor / group / supervised
							aerobic exercise	vigorous	3x 60min / week	23%	outpatient / indoor / group / supervised

Notes: ‡ we received additional information from authors; † we received corrections from authors; [+] we extracted data extracted from graphs; [a] dissertation thesis;
Abbreviations: TAU = treatment as usual; CBT = cognitive behavioral treatment; SSRI = selective serotonin reuptake inhibitor; KKW = kilocalories per kilogram body weight per week; PSQI = Pittsburgh Sleep Quality Index; HAMD = Hamilton Rating Scale for Depression; IDS-C = Inventory of Depressive Symptomatology Clinician Version; ISI = Insomnia Severity Index;

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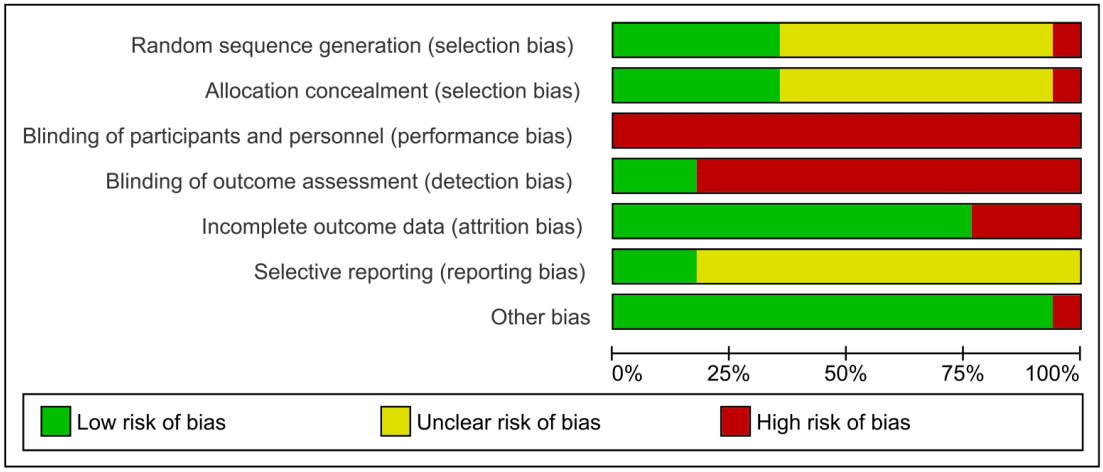
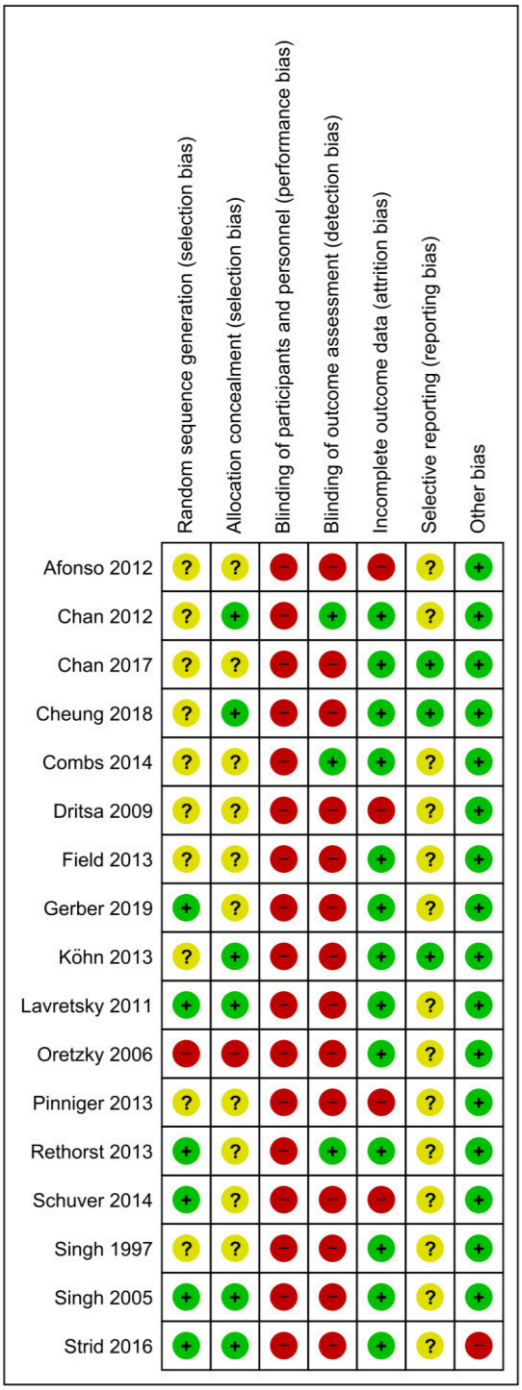
Section 5: Risk of bias in included trials

We strictly applied the criteria defined in the tool, i.e., considering a lack of participant blinding (which is impossible in exercise trials) and the use of self-report questionnaires as a high risk of performance and detection bias, respectively. Selective reporting bias was assessed by comparing protocols (if available) and reports of trials.

5a: Risk of bias in all trials



5b: Risk of bias in each trial



Section 6: Local inconsistency

Output from the netsplit command comparing the estimated treatment effect derived from the network meta-analysis, direct, and indirect evidence

Comparison	k	prop	nma	direct	indirect	diff.	z	p
Active control : light strength	1	0.44	0.19	-0.02	0.36	-0.38	-0.75	0.45
Active control : meditation	1	0.82	-0.13	-0.13	-0.14	0.01	0.02	0.99
Active control : mind-body	1	0.19	0.00	0.35	-0.08	0.43	1.03	0.31
Active control : passive control	2	0.45	-0.44	-0.39	-0.49	0.10	0.30	0.76
Active control : TAU	1	0.5	0.04	-0.06	0.14	-0.20	-0.68	0.50
Active control : vigorous aerobic	1	0.69	0.06	0.00	0.20	-0.20	-0.60	0.55
Active control : vigorous strength	1	0.43	0.65	0.81	0.53	0.28	0.54	0.59
Light strength : meditation	1	0.82	-0.32	-0.11	-1.28	1.17	1.19	0.23
Light strength : passive control	1	0.48	-0.63	-0.30	-0.93	0.63	1.25	0.21
Light strength : TAU	1	0.50	-0.15	-0.38	0.09	-0.47	-0.97	0.33
Light strength : vigorous strength	1	0.70	0.46	0.25	0.94	-0.69	-1.10	0.27
Meditation : passive control	1	0.87	-0.31	-0.20	-1.11	0.91	0.88	0.38
Mind-body : moderate aerobic	1	0.61	-0.13	-0.04	-0.27	0.23	0.69	0.49
Mind-body : passive control	4	0.81	-0.44	-0.47	-0.31	-0.16	-0.62	0.53
Mind-body : TAU	1	0.65	0.04	0.11	-0.09	0.20	0.76	0.45
Mind-body : vigorous aerobic	1	0.58	0.06	0.13	-0.04	0.18	0.57	0.57
Mind-body + TAU : passive control	1	0.30	-0.94	-1.03	-0.91	-0.12	-0.26	0.80
Mind-body + TAU : TAU	3	0.95	-0.46	-0.43	-1.00	0.57	0.73	0.47
Moderate aerobic : passive control	1	0.41	-0.31	-0.24	-0.36	0.11	0.36	0.72
Moderate aerobic : TAU	1	0.78	0.17	0.16	0.23	-0.08	-0.22	0.83
Moderate aerobic : vigorous aerobic	1	0.68	0.19	0.18	0.23	-0.05	-0.14	0.89
Moderate aerobic + TAU : TAU	1	0.48	-0.08	-0.39	0.22	-0.61	-1.25	0.21
Moderate aerobic + TAU : vigorous aerobic + TAU	1	0.67	0.10	0.31	-0.31	0.61	1.25	0.21
Passive control : TAU	1	0.13	0.48	0.82	0.43	0.38	0.97	0.33
TAU : vigorous aerobic	2	0.95	0.02	0.04	-0.31	0.34	0.67	0.50
TAU : vigorous aerobic + TAU	1	0.85	0.18	0.09	0.70	-0.61	-1.25	0.21
TAU : vigorous strength	1	0.58	0.61	0.64	0.57	0.06	0.12	0.91
TAU : vigorous strength	1	0.58	0.61	0.64	0.57	0.06	0.12	0.91

Abbreviations: k = Number of studies providing direct evidence; prop = direct evidence proportion; nma = estimated treatment effect (SMD) in network meta-analysis; direct = estimated treatment effect (SMD) derived from direct evidence; indirect = estimated treatment effect (SMD) derived from indirect evidence; diff. = difference between direct and indirect treatment estimates; z = z-value of test for disagreement (direct versus indirect); p-value = p-value of test for disagreement (direct versus indirect); TAU = treatment as usual.
Note that the direct evidence presented here might differ from the evidence presented in the upper half of the league table, since the latter is based on pair-wise meta-analysis.

Section 7: Individual treatment effects of all included trials

Trial	Comparator 1	Comparator 2	SMD	SE	SE adjusted for multi-arm trials	N arms for each trial	Multiarm trial
Singh 2005	light strength	vigorous strength	0.25	0.34	0.42	3	yes
Singh 2005	TAU	vigorous strength	0.64	0.34	0.41	3	yes
Singh 2005	light strength	TAU	-0.38	0.34	0.41	3	yes
Lavretsky 2011	mind-body + TAU	TAU	-0.25	0.24	0.24	2	no
Combs 2014	active control	vigorous aerobic	0.00	0.17	0.2	3	yes
Combs 2014	TAU	vigorous aerobic	0.06	0.17	0.2	3	yes
Combs 2014	active control	TAU	-0.06	0.2	0.29	3	yes
Chan 2012	mind-body + TAU	passive control	-1.03	0.37	0.47	3	yes
Chan 2012	mind-body + TAU	TAU	-0.21	0.34	0.4	3	yes
Chan 2012	passive control	TAU	0.82	0.36	0.45	3	yes
Oretzky 2007	mind-body	passive control	-0.95	0.29	0.29	2	no
Cheung 2018	moderate aerobic + TAU	TAU	-0.39	0.35	0.35	2	no
Rethorst 2013	TAU	vigorous aerobic + TAU	0.09	0.18	0.18	2	no
Schuver 2014	mind-body	moderate aerobic + HE	0.46	0.35	0.35	2	no
Pinniger 2013	active control	light strength	-0.02	0.37	0.54	4	yes
Pinniger 2013	light strength	meditation	-0.11	0.42	0.7	4	yes
Pinniger 2013	light strength	passive control	-0.3	0.36	0.49	4	yes
Pinniger 2013	active control	passive control	-0.33	0.32	0.4	4	yes
Pinniger 2013	meditation	passive control	-0.2	0.37	0.5	4	yes
Pinniger 2013	active control	meditation	-0.13	0.38	0.57	4	yes
Dritsa 2009	moderate aerobic	passive control	-0.24	0.24	0.24	2	no
Field 2013	mind-body	passive control	-0.45	0.23	0.23	2	no
Gerber 2019	moderate aerobic + TAU	vigorous aerobic + TAU	0.31	0.28	0.28	2	no
Köhn 2013	mind-body + TAU	TAU	-1.04	0.35	0.35	2	no
Singh 1997	active control	vigorous strength	0.81	0.4	0.4	2	no
Strid 2016	mind-body	TAU	0.11	0.15	0.17	4	yes
Strid 2016	moderate aerobic	TAU	0.16	0.15	0.17	4	yes
Strid 2016	TAU	vigorous aerobic	0.02	0.15	0.16	4	yes
Strid 2016	mind-body	moderate aerobic	-0.04	0.2	0.42	4	yes
Strid 2016	mind-body	vigorous aerobic	0.13	0.19	0.4	4	yes
Strid 2016	moderate aerobic	vigorous aerobic	0.18	0.2	0.42	4	yes
Afonso 2012	active control	passive control	-0.47	0.38	0.46	3	yes
Afonso 2012	mind-body	passive control	-0.83	0.38	0.47	3	yes
Afonso 2012	active control	mind-body	0.35	0.37	0.46	3	yes
Chan 2016	mind-body	passive control	-0.29	0.15	0.15	2	no

Abbreviations: SMD = standardized mean difference; SE = standard error, HE = health education; TAU = treatment as usual.

Section 8: Confidence in the findings of the network meta-analysis

We evaluated the confidence in the findings of the network meta-analysis using the CINeMA tool [1] which is based on the GRADE approach [2].

Assessments are based on the following criteria and rules:

1. Within-study bias: We downgraded all comparisons by one level, since overall risk of bias per trial was high in all trials.
2. Reporting bias: Assessing the likelihood of publication or small study bias is difficult [3]. We performed a very thorough and systematic search including multiple databases, grey literature, and protocols. We did not detect any reporting bias.
3. Indirectness: Assessment of indirectness for each arm can be found in Section 1. The table below shows the average indirectness per comparison. We downgraded if major or some concerns were present.
4. Imprecision: We considered a clinically meaningful threshold for SMD to be 0.5. We downgraded if major or some concerns were present.
5. Heterogeneity: We downgraded if prediction interval extended into clinically important or unimportant effects.
6. Incoherence: We did not detect any local or global incoherence (see article and Section 6). Thus, we did not downgrade any comparison.

The table below lists assessments by comparison. Confidence was moderate (43% of comparisons), low (39% of comparators) or very low (18% of comparisons).

References

[1] CINeMA: Confidence in Network Meta-Analysis. Institute of Social and Preventive Medicine, University of Bern; 2017.

[2] Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2014;349. https://doi.org/10.1136/bmj.g5630.

[3] Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011;64:1277–82. https://doi.org/10.1016/j.jclinepi.2011.01.011.

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
active CONT:TAU	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
light strength:TAU	1	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
mind-body:TAU	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mind-body + TAU:TAU	3	Major concerns	Undetected	Some	No concerns	No concerns	No concerns	Low
mod. aerobic:TAU	1	Major concerns	Undetected	No concerns	No concerns	Some	No concerns	Low
mod. aerobic + TAU:TAU	1	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
passive CONT:TAU	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
TAU:vig. aerobic	2	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
TAU:vig. aerobic + TAU	1	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
TAU:vig. strength	1	Major concerns	Undetected	Some	No concerns	No concerns	No concerns	Low
active CONT:light strength	1	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
active CONT:meditation	1	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
active CONT:mind-body	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
active CONT:passive CONT	2	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
active CONT:vig. aerobic	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
active CONT:vig. strength	1	Major concerns	Undetected	Some	No concerns	No concerns	No concerns	Low
light strength:meditation	1	Major concerns	Undetected	No concerns	Some	Some	No concerns	Very low
light strength:passive CONT	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
light strength:vig. strength	1	Major concerns	Undetected	Major	Some	No concerns	No concerns	Very low
meditation:passive CONT	1	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mind-body:mod. aerobic	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mind-body:mod. aerobic + HE	1	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mind-body:passive CONT	4	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mind-body:vig. aerobic	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mind-body + TAU:passive CONT	1	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mod. aerobic:passive CONT	1	Major concerns	Undetected	No concerns	No concerns	Some	No concerns	Low
mod. aerobic:vig. aerobic	1	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mod. aerobic + TAU:vig. aerobic +	1	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
Indirect evidence								
meditation:TAU	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
mod. aerobic + HE:TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
active CONT:mind-body + TAU	0	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
active CONT:mod. aerobic	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
active CONT:mod. aerobic + HE	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
active CONT:mod. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	Some	No concerns	Very low
active CONT:vig. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
light strength:mind-body	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
light strength:mind-body + TAU	0	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
light strength:mod. aerobic	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
light strength:mod. aerobic + HE	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
light strength:mod. aerobic + TAU	0	Major concerns	Undetected	Some	Major	No concerns	No concerns	Very low
light strength:vig. aerobic	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
light strength:vig. aerobic + TAU	0	Major concerns	Undetected	Some	Major	No concerns	No concerns	Very low
meditation:mind-body	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
meditation:mind-body + TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
meditation:mod. aerobic	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
meditation:mod. aerobic + HE	0	Major concerns	Undetected	No concerns	Some	Some	No concerns	Very low
meditation:mod. aerobic + TAU	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
meditation:vig. aerobic	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
meditation:vig. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	Some	No concerns	Very low
meditation:vig. strength	0	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
mind-body:mind-body + TAU	0	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mind-body:mod. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mind-body:vig. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mind-body:vig. strength	0	Major concerns	Undetected	Some	No concerns	No concerns	No concerns	Low
mind-body + TAU:mod. aerobic	0	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mind-body + TAU:mod. aerobic +	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
mind-body + TAU:mod. aerobic +	0	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
mind-body + TAU:vig. aerobic	0	Major concerns	Undetected	No concerns	No concerns	Some	No concerns	Low
mind-body + TAU:vig. aerobic +	0	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
mind-body + TAU:vig. strength	0	Major concerns	Undetected	Some	Some	Some	No concerns	Very low
mod. aerobic:mod. aerobic + HE	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mod. aerobic:mod. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mod. aerobic:vig. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mod. aerobic:vig. strength	0	Major concerns	Undetected	Some	No concerns	No concerns	No concerns	Low
mod. aerobic + HE:mod. aerobic +	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
mod. aerobic + HE:passive CONT	0	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
mod. aerobic + HE:vig. aerobic	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
mod. aerobic + HE:vig. aerobic +	0	Major concerns	Undetected	No concerns	Major	No concerns	No concerns	Low
mod. aerobic + HE:vig. strength	0	Major concerns	Undetected	Some	Major	No concerns	No concerns	Very low
mod. aerobic + TAU:passive	0	Major concerns	Undetected	No concerns	No concerns	Some	No concerns	Low
mod. aerobic + TAU:vig. aerobic	0	Major concerns	Undetected	No concerns	Some	Some	No concerns	Very low
mod. aerobic + TAU:vig. strength	0	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low
passive CONT:vig. aerobic	0	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
passive CONT:vig. aerobic + TAU	0	Major concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
passive CONT:vig. strength	0	Major concerns	Undetected	Some	No concerns	No concerns	No concerns	Low
vig. aerobic:vig. aerobic + TAU	0	Major concerns	Undetected	No concerns	Some	No concerns	No concerns	Low
vig. aerobic:vig. strength	0	Major concerns	Undetected	Some	No concerns	Some	No concerns	Very low
vig. aerobic + TAU:vig. strength	0	Major concerns	Undetected	Some	Some	No concerns	No concerns	Very low

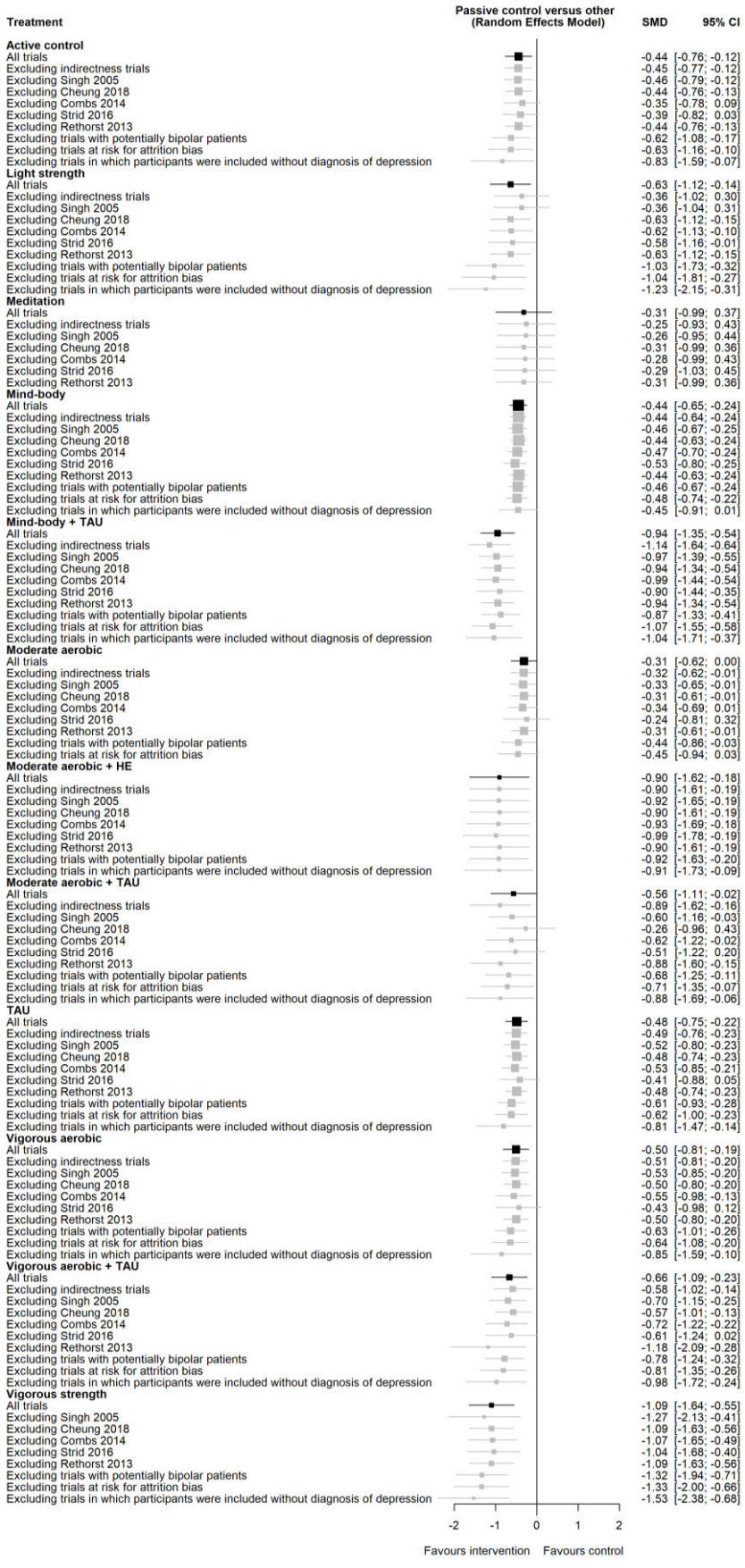
Abbreviations: SMD = standardized mean difference; SE = standard error, mod. = moderate, vig. = vigorous; HE = health education; TAU = treatment as usual; CONT = control.

Section 9: Sensitivity analyses

We performed multiple sensitivity analysis: excluding trials with (1) a high risk of indirectness, (2) trials for which we had to perform preprocessing with additional assumptions which we could not verify, (3) trials which did not explicitly state that bipolar patients were excluded, (4) trials which were considered to have a high risk of attrition bias, and (5) trials which did not base inclusion on a formal diagnosis of depression (i.e. according to DSM or ICD), see Figure 9a.

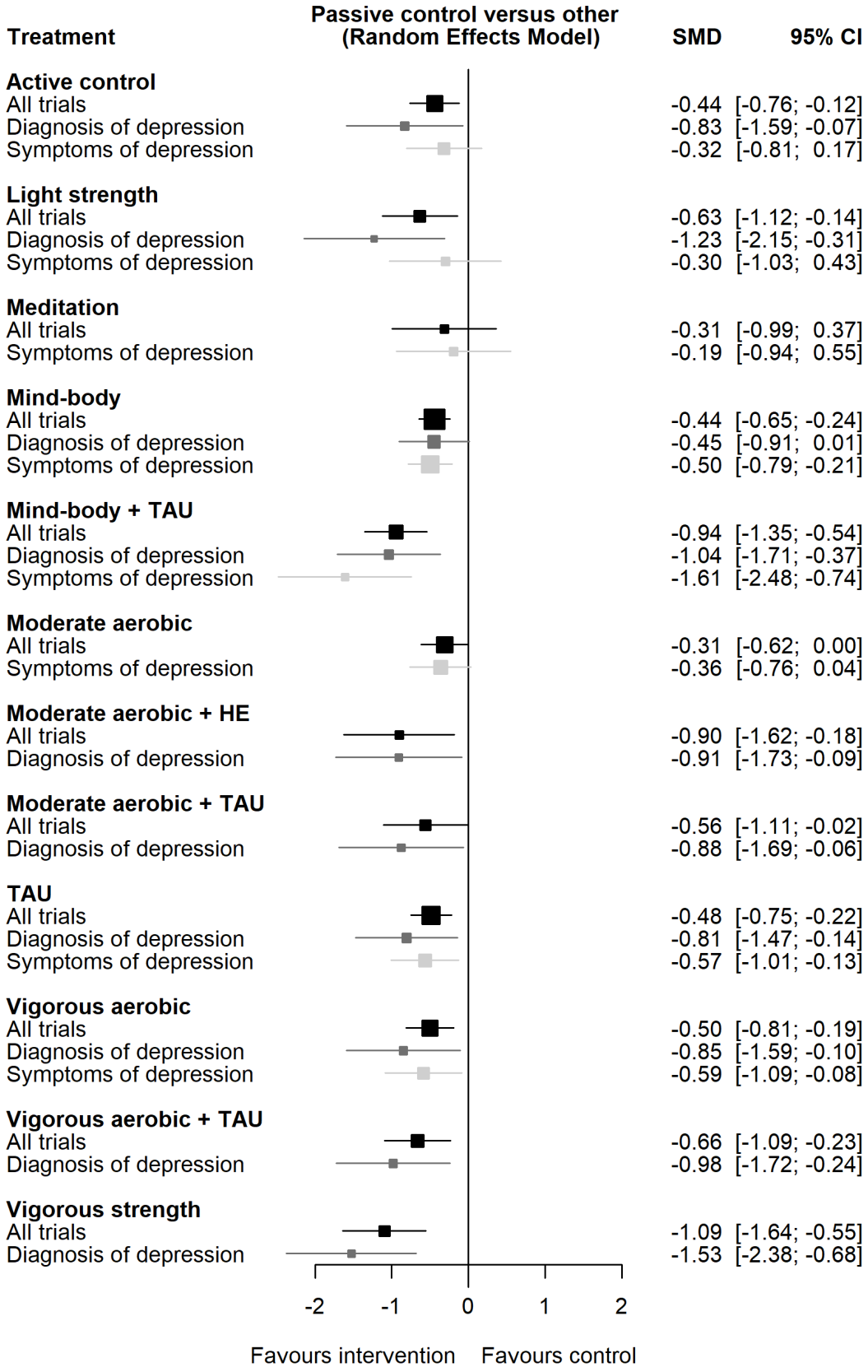
Furthermore, we compare the network meta-analysis effect size estimates of all trials, only those trials which included participants based on depression diagnosis, and only those trials which included participants based on depression symptoms, see Figure 9b.

9a: Network meta-analysis effect size estimates excluding specific trials



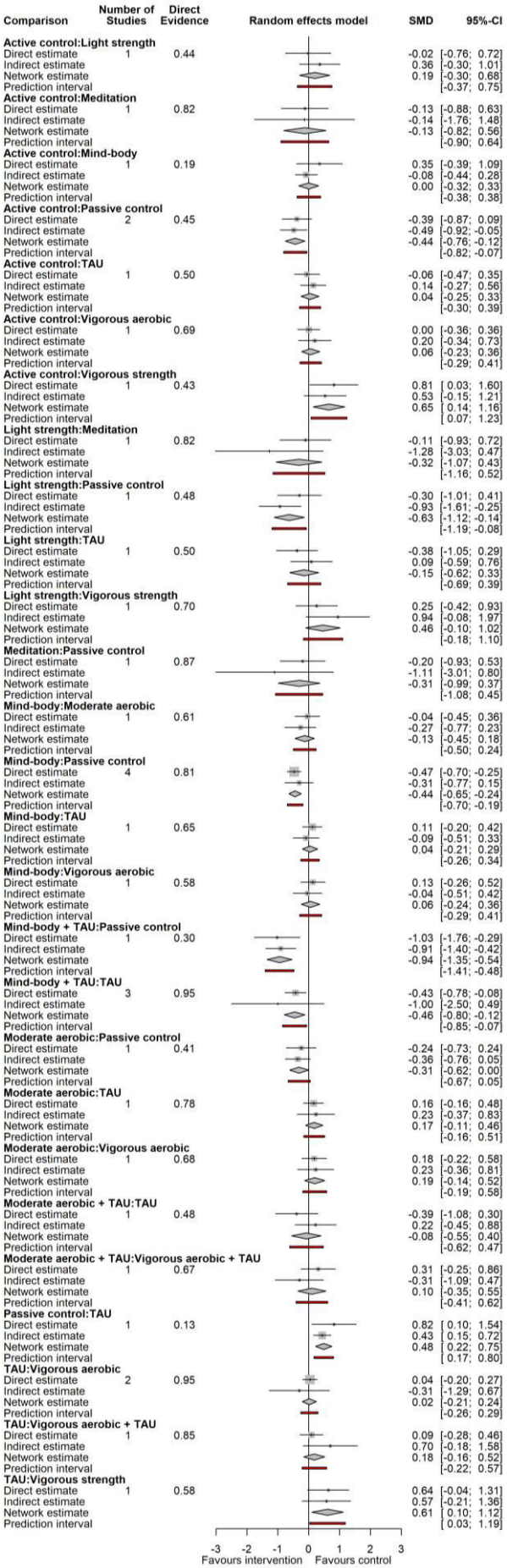
Abbreviations: HE = health education; TAU = treatment as usual

9b: Network meta-analysis effect size estimates based on all trials and trials which included participants based on depression diagnosis or depression symptoms



Abbreviations: HE = health education; TAU = treatment as usual

Section 10: Direct, indirect, and network estimates with prediction intervals



Abbreviations: TAU = treatment as usual.

Note that the direct evidence presented here might differ from the evidence presented in the upper half of the league table, since the latter is based on pair-wise meta-analysis.

Chapter 5

Publication 3: The acute effects of aerobic exercise on sleep in patients with depression: study protocol for a randomized controlled trial

Authors:

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Trials

STUDY PROTOCOL Open Access

The acute effects of aerobic exercise on sleep in patients with depression: study protocol for a randomized controlled trial

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Abstract

Background: Unipolar depression is one of the most important mental disorders. Insomnia is a symptom of cardinal importance in depression. It increases the risk to develop depression, negatively affects disease trajectory, is the most common symptom after remission, increases the risk of relapse, and is associated with higher suicide rates. Existing therapies for insomnia in depression have limitations. Further adjuvant therapies are therefore needed. Acute aerobic exercise has been shown to have beneficial effects on sleep in healthy individuals and patients with insomnia. We therefore hypothesize that a single session of aerobic exercise has a positive impact on sleep in patients with unipolar depression. This trial aims to investigate the effects of a single bout of aerobic exercise on the subsequent night's sleep in patients with depression.

Methods/design: This is a two-arm parallel group, randomized, outcome assessor blinded, controlled, superiority trial. Patients between 18 and 65 years of age with a primary diagnosis of unipolar depression (without a psychotic episode) are included. Exclusion criteria are regular use of hypnotic agents, opioids, and certain beta-blockers, as well as the presence of factors precluding exercise, history of epilepsy, restless legs syndrome, moderate obstructive sleep apnea, and a BMI > 40. The intervention is a single bout of aerobic exercise, performed for 30 min on a bicycle ergometer at 80% individual anaerobic threshold. The control group sits and reads for 30 min. The primary outcome is sleep efficiency measured by polysomnography. Secondary outcomes include further polysomnographic variables, subjective pre-sleep arousal, nocturnal cardiovascular autonomic modulation, subjective sleep quality, daytime sleepiness, and adverse events. According to the sample size calculation, a total of 92 patients will be randomized using minimization.

Discussion: This trial will add new information to the body of knowledge concerning the treatment of insomnia in patients with depression. Thereby, the results will inform decision makers on the utility of acute aerobic exercise.

Trial registration: Clinicaltrials.gov, NCT03673397. Protocol version 1 registered on 17 September 2018.

Keywords: Exercise, Depression, Sleep, Polysomnography, Heart rate variability, Blood pressure, Randomized controlled trial, Protocol

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Background

Unipolar depression is a mental disorder of paramount importance. Worldwide the lifetime prevalence is estimated to be between 10 and 15% [1]. It is projected to become the leading cause of burden of disease worldwide by 2030 [2]. Core symptoms of depression are depressed mood, anhedonia, and a lack of drive. Depression is associated with an increased risk of comorbidities [3] and cardiovascular mortality [4]. It is also associated with lower cardiorespiratory fitness [5], an independent risk factor for cardiovascular mortality in healthy individuals [6].

There is a plethora of research concerning treatments for depression. Psychotherapy, pharmacotherapy or a combination of both are the primary treatments for depression according to guidelines [7, 8]. Meta-analytic data show moderate to large effect sizes for pharmacotherapy (0.35), psychotherapy (0.37), and combined therapy (0.74) when compared to placebo [9]. However, the STAR*D trial investigating four treatment steps in over 4000 patients concluded that only two-thirds of people treated for depression with pharmacotherapy, cognitive behavioral therapy, or both were in remission after treatment [10]. Moreover, the majority of patients tend to prefer non-pharmacological treatments for insomnia [11, 12] and depression [13]. Hence, there is a need for further adjuvant non-pharmacological treatment options.

Insomnia encompasses problems initiating or maintaining sleep with daytime impairments [14]. Another symptom may be non-restorative sleep. The current state of knowledge suggests that hyperarousal [15, 16], as well as sleep reactivity [17], are core etiological factors of insomnia. Hyperarousal can be cognitive (e.g., rumination, dysfunctional beliefs), emotional (emotional reactivity), cortical (beta activity in sleep EEG), or physiological (e.g., metabolic rate, heart rate variability).

There is an abundance of research related to insomnia treatments. Cognitive behavioral therapy for insomnia (CBT-I) and pharmacotherapy are currently considered first- and second-line therapies for insomnia (regardless whether comorbidities are present or not) [17, 18]. CBT-I is very effective [19]. However, the number of trained specialists considerably limits access to this treatment. Pharmacologic agents such as benzodiazepines, non-benzodiazepines, and sedating antidepressants are another, arguably more frequently administered therapy for insomnia. However, pharmacotherapy has multiple limitations: (1) effects have been shown to be statistically significant but of limited clinical relevance [20, 21], (2) dosages and (3) prescription duration frequently exceed recommendations of health agencies [22, 23] (especially in patients with comorbidities [24, 25]), (4) it potentially has severe adverse effects [26–28], and (5) patients often prefer non-pharmacological therapies [11, 29, 30]. Therefore, there is a need to develop further non-pharmacological treatments.

Insomnia is a highly relevant symptom of depression. Depending on the methodological approach, studies have found 25–90% prevalence rates of insomnia in people with depression [31, 32]. Longitudinal studies have repeatedly found a bidirectional link between insomnia and depression [33–36]. Insomnia is of prognostic relevance. It negatively affects the disease trajectory [37], is the most frequent residual symptom after treatment response or remission [31, 38, 39], increases the probability of relapse [37, 40, 41], and is an independent risk factor for suicide [42, 43] as well as adverse somatic outcomes, particularly cardiovascular disease [44]. Insomnia has considerable economic cost. Individuals who have insomnia are at higher risk for work presenteeism [45, 46] and absenteeism [47] with higher direct costs per short-term absence [48]. Sleep problems are also associated with more work injuries [49]. Insomnia increases the risk of ending employment prematurely [50] and increases the risk of disability retirement due to depression [51].

Insomnia of depressed individuals has been neglected in research, despite its known relevance. Until approximately one decade ago, a central etiological distinction was made between 'organic' and 'psychogenic' or 'primary' and 'secondary' insomnia [52]. However, this distinction has been challenged because, among other reasons, there is often a lack of evidence for a mechanistic distinction between primary and secondary insomnia [52]. Therefore, a paradigm shift has become apparent, recommending specific treatments for comorbid insomnia. This paradigm shift might explain why, until recently, most trials have focused on patients with insomnia without any comorbidities.

Aerobic exercise is a viable candidate for the treatment of insomnia in patients for depression. Meta-analyses have shown a positive impact of acute and chronic exercise in healthy individuals with small to moderate effect sizes [53, 54]. Meta-analyses focusing on individuals with at least mild insomnia but no comorbidities have found a moderate effect of chronic aerobic exercise on sleep quality [54–56]. Aerobic exercise has further positive effects such as improving depressive symptoms [57] and cardiorespiratory fitness [58]. The latter is especially relevant for the reduction of cardiovascular risk [6].

Current sleep hygiene recommendations, which are also relevant for depression, lack feasibility. In particular, they state that exercise should not be performed after 2 pm [59]. This time constraint presents a considerable limitation since many people can only accommodate aerobic exercise in the late afternoon or evening. Even more so this may be limiting for patients with morning depression

who may feel more energetic to exercise in the afternoon [60]. However, a recent meta-analysis has found equivocal effects of exercise performed in the afternoon or evening in healthy individuals [54]. In healthy individuals, effects of a single evening bout of aerobic exercise on nocturnal heart rate variability seem to depend on intensity, duration, and timing relative to sleep but do not seem to alter subjective sleep quality [61, 62]. One trial has investigated the effects of acute aerobic exercise in chronic primary insomniacs, showing moderate to large effect sizes for shortened sleep onset latency, improved sleep efficiency, and longer total sleep time [63].

Rationale and hypotheses

An extensive literature search yielded no randomized controlled trials investigating the acute effects of exercise on sleep in patients with depression. Several studies concerned with chronic effects are available, and we will summarize these in our upcoming systematic review and network meta-analysis (PROSPERO ID 115705, registration not published yet). Considering this gap in the literature and the uncertainty concerning the effects of exercise performed in the afternoon on sleep in patients with depression, a trial on this topic is of high clinical importance.

We hypothesize that an acute bout of aerobic exercise improves 1) sleep efficiency [54, 63], 2) sleep continuity [63], 3) sleep architecture [54], 4) subjective sleep quality [64], 5) daytime sleepiness [65], 6) nocturnal blood pressure [66], 7) pre-sleep arousal, and 8) pre- and post-sleep heart-rate variability. We expect no effect on 9) nocturnal heart rate variability [62] and 10) the frequency and severity of adverse events [64].

This paper presents the design and protocol for the trial according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [67] (Additional file 1).

Methods/design

Study design and setting

This study is designed as a two-arm parallel group, randomized, outcome assessor blinded, controlled trial, to assess the superiority of (i) an acute bout of aerobic exercise compared to (ii) control in ameliorating sleep efficiency in patients with depression (Fig. 1).

The trial is conducted in the psychosomatic inpatient rehabilitation unit of the OBERWAID AG, a rehabilitation clinic in St. Gallen, Switzerland. Patients are referred to the clinic by their general practitioner or a psychiatrist. On average, approximately 250 patients with a primary diagnosis of an ICD-10 depressive episode without psychotic features are referred to the clinic annually. The OBERWAID AG also offers outpatient psychosomatic care, cardiovascular inpatient rehabilitation, and orthopedic aftercare.

Participants

Eligibility criteria

Patients aged 18–65 years with a diagnosis of depression (confirmed by experienced psychiatrists according to ICD-10) undergoing inpatient psychosomatic rehabilitation in the OBERWAID clinic are eligible for inclusion.

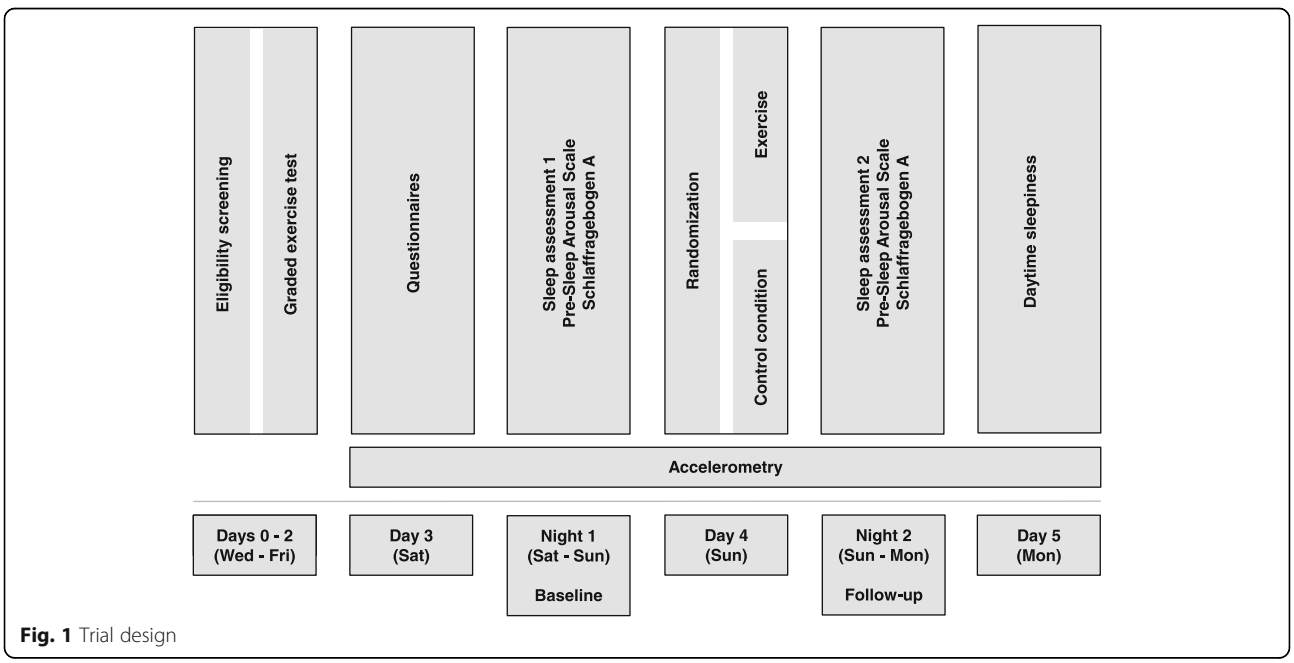

Fig. 1 Trial design

Further inclusion and exclusion criteria with corresponding rationales are listed in Table 1.

Recruitment

Patients are given the study information at the preliminary medical consultation, which takes place approximately 3 weeks (but no later than 2 days) before admission. On the day of admission, the clinical trial is presented to the patients by the study coordinator. Patients who are interested in participating in the study can ask the study coordinator questions directly. In order to ensure adequate time to consider their participation, interested and potentially eligible patients meet the study coordinator for an informed discussion again on the following day (i.e., the first day after admission). The study coordinator obtains the written informed consent from patients willing to participate. Should the study coordinator be absent, his designated replacement obtains the informed consent. The information sheet and consent form are in German (Additional file 2). It is clinical routine for the leading physicians to give all patients a general consent form.

Table 1 Inclusion and exclusion criteria

Criterion	Rationale
Inclusion criteria	
≥ 18 and ≤ 65 years old	Results of the trial should be generalizable to the working age population. Furthermore, there can be numerous reasons for sleep disorders in older patients [68]
Primary diagnosis of depression (F32, F33) without psychotic episode according to ICD-10	Mental disorder used to define the sample
Exclusion criteria	
Regular use of hypnotic agents* (patients are included if no hypnotic agents were taken two weeks before study participation)	Use of hypnotic agents might mask the effect of aerobic exercise on sleep
Factors precluding exercise testing or training	For safety reasons, patients who have any condition which precludes exercise testing or training are excluded. Absolute and relative contraindications are based on ACSM's Guidelines for Exercise Testing and Prescription [69]
Use of beta-blockers (except carvedilol and nebivolol)	Except for carvedilol and nebivolol [70, 71], beta-blockers have been shown to reduce nocturnal melatonin levels [70, 72, 73]
Use of opioids	Opioids affect sleep architecture [74]
History of epilepsy	Epilepsy is associated with quantitative and qualitative alterations of sleep [75] and might, therefore, mask the intervention effects
Restless legs syndrome defined by ≥ 7 points on the restless legs screening questionnaire [76]	Can also cause sleep disturbance, but the etiology is distinct from depression [77]
Moderate or severe sleep apnea defined by an oxygen desaturation index (ODI) ≥ 15 in the first polysomnography	Sleep apnea is a distinct sleep disorder with clearly delineated etiology. ODI has been shown to be highly correlated with the apnea-hypopnea index and to detect sleep apnea with high sensitivity and specificity [78–80]
Morbid adiposity with BMI > 40	These patients might suffer from hypoventilation syndrome which affects sleep

ICD-10 International Classification of Diseases, version 10, *ODI* oxygen desaturation index, *BMI* body mass index
*Hypnotic agents are defined as follows: orexin receptor agonists, benzodiazepine receptor agonists, sedating antidepressants, neuroleptics, benzodiazepines, melatonin agonists, heterocyclics, anticonvulsants, over the counter sleep aids (sedating antihistamines, melatonin L-tryptophan, valerian), and cannabinoids

Retention

Appointments for data collection are included in the therapy schedule during the first 6 days of rehabilitation, which should reduce the burden on patients and ensure protocol fidelity. We give patients feedback on their measurements. We will send a digital copy of publications based on this trial to participants if they have chosen to receive one. No monetary compensation is offered for participation.

Withdrawal, discontinuation, and stopping rules

Participants can withdraw from the trial at any time without having to provide reasons. If possible, we collect follow-up data and reasons for withdrawal. Patients can be withdrawn from the trial by the principal investigator for medical reasons (e.g., transfer to another hospital). Exercise testing and training is immediately stopped, should any indications for exercise test termination, as defined by the American College of Sports Medicine, be met [69]. In this case, we collect follow-up data if there are no contraindications.

Measurements and procedure

Rationale for measurements

This section offers a rationale for the selected variables and performed measurements. Details of each assessment (measurement variable, reliability, validity, analysis metric, method of aggregation, time point, and clinical relevance) are provided below.

Baseline This trial does not exclude patients with psychiatric comorbidities in order to preserve external validity. Therefore, we perform an extensive baseline characterization of the sample (Fig. 2). The characterization consists of questionnaires on psychiatric, somatic, and insomnia-specific symptom severity as well as sleep-related variables such as chronotype and sleep-related cognitions. Furthermore, baseline

	STUDY PERIOD					
	Screening	Background	Baseline	Allocation	Intervention	Follow-up
TIMEPOINT**	$-t_3$	$-t_2$	$-t_1$	t_0	t_1	t_2
Days after admission	0 - 2	3	3 - 4	4	4	4 - 5
ENROLMENT:						
Information	X					
Informed consent	X					
Eligibility screening	X					
Allocation				X		
INTERVENTIONS:						
Aerobic exercise					X	
Control					X	
ASSESSMENTS:						
*Graded exercise test **	X					
Patient Health Questionnaire (PHQ-9)		X				
*Hospital Anxiety & Depression Questionnaire**		X				
Perceived Stress Scale		X				
*Patient Health Questionnaire (PHQ-15)**		X				
*Cumulative Illness Rating Scale**		X				
Epworth Sleepiness Scale		X				
*Pittsburgh Sleep Quality Index**		X				
Dysfunctional beliefs & attitudes about sleep scale		X				
Ford Insomnia Response to Stress Test		X				
Morningness-Eveningness Questionnaire		X				
Expectancy and Credibility (single items)		X				
*Polysomnography**			X*			X
Pre-Sleep Arousal Scale			X			X
Schlaffragebogen A, 'subjective sleep scale'			X			X
Stanford Sleepiness Scale						X
Heart rate					X	
Rate of perceived exertion					X	
Befindlichkeitsskala, 'mood scale'					X	
Actigraphy		◆	———	———	———	◆

*These measurements are performed as part of the clinical routine

Fig. 2 Participant timeline - Spirit figure

polysomnography will provide an extensive characterization of sleep.

Primary outcome Sleep disorders are of complex etiology and have various psycho-physiological consequences. Therefore, it is recommended to measure the effects of interventions on insomnia symptoms as well as other factors such as daytime functioning and mood [81]. Insomnia can be classified into sleep-onset, sleep-maintenance, and sleep-offset

subtypes. Meta-analysis of polysomnographic data has shown that patients with depression and other mental health disorders have mixed (i.e., sleep-onset and sleep-maintenance) insomnia [82]. Sleep efficiency best captures both of these aspects and is therefore chosen as the primary outcome. Objective quantification of the primary outcome is vital in this study since the blinding of participants is not possible, thereby potentially affecting subjective measurements.

Secondary outcomes Secondary outcomes which inform clinical decision making include further polysomnographic variables, subjective pre-sleep arousal, cardiovascular autonomic modulation, subjective sleep quality, daytime sleepiness, and adverse events. Wake after sleep onset and number of awakenings identify sleep-maintenance insomnia, while sleep-onset latency characterizes sleep-onset insomnia.

Patients with depression show characteristic changes in rapid eye movement (REM) latency (time between sleep onset and first rapid eye movement sleep episode), REM-density (frequency of rapid eye movements/REM episode), and duration of REM sleep (collectively known as REM pressure) [82]. More importantly, these alterations have a negative impact on treatment and increase the risk of relapse [83]. Exercise has been shown to reduce REM sleep and increase slow wave sleep [54]. The discrepancy between objective and subjective sleep measurements is well documented [81, 84, 85]. Therefore, we measure the subjective sleep quality of the previous night in addition to the objective sleep assessment. Patient views influence the treatment of sleep disorders [86, 87]. Hence, it is crucial to ascertain the credibility of the intervention and the expectancy of participants. Adverse events are underreported in sleep trials but highly relevant to clinical decision making [88]. The case report form specifically captures adverse events (see below) to gauge the benefit to harm ratio.

Screening

After providing informed consent, we formally screen patients for inclusion and exclusion criteria of this study. They are consulted by an experienced psychiatrist and undergo a full history and medical examination by an experienced internist, including vital parameters. (Resting electrocardiogram may be forgone if the general practitioner of the patient provides one no older than 2 months.) Patients with undiagnosed sleep apnea are excluded according to the baseline polysomnography (see below).

Graded exercise testing

Patients fulfilling all eligibility criteria (except the sleep apnea criterion, which is determined later by polysomnography) undergo sub-maximal graded exercise testing on a bicycle ergometer (ergoselect 200, Ergoline, Bitz, Germany). The goal is to determine the individual anaerobic threshold. The anaerobic threshold is used to standardize the exercise intensity of the intervention across patients. Since subjects vary in their endurance capacity and weight, we adjust initial and subsequent work rates (Watts) between subjects before the test. Stage duration is always 3 minutes, as this has been found to yield the most reliable and valid results [89]. We measure blood lactate at the end of each stage using capillary blood from the earlobe. We assess blood lactate level with Lactate Scout+ (SensLab GmbH, Leipzig, Germany), a validated hand-held analyzer [90]. Heart rate is measured using the validated Polar® H7 chest strap (Polar OY, Finland) [91]. Parasympathetic drive is still present at lower exercise intensities and thus increases heart rate variability [92]. The average heart rate during the last 30 s of each stage is extracted to improve precision and used for further analyses. Ratings of perceived exertion are recorded at the end of each stage according to Borg's 6–20 scale [93]. The graded exercise test data are analyzed using a specialized software program (Ergonizer, Freiburg, Germany). The individual anaerobic threshold is determined according to the method of Dickhuth et al. [94].

Baseline characterization of symptom severity

To characterize the study population in detail, we will report multiple continuous measures at baseline as median with corresponding interquartile range or frequencies.

Somatic and psychological symptom severity In accordance with the International Consortium for Health Outcomes Measurement (ICHOM) Depression and Anxiety working group, depression symptoms are assessed with the German version of the Patient Health Questionnaire-9 (PHQ-9) including the additional question on functioning [95]. The nine symptom items are scored on a four-point Likert scale (*not at all* to *nearly every day*; Cronbach's $\alpha = 0.89$). The cut-offs of the aggregated sum score have been validated and allow for classification of mild to severe depression [96]. Anxiety is assessed using the Hospital Anxiety and Depression Scale. This questionnaire measures depression and anxiety with seven items each on a four-point Likert scale [97]. A meta-analysis has found Cronbach's α to be 0.83 and 0.82 for the anxiety and depression subscales, respectively [98]. Diagnostic test accuracy of the depression and anxiety subscale is high [99]. More recently, a meta confirmatory factor analysis has suggested the presence of a general distress factor explaining most of the covariance between items [100]. The German version has been shown to have adequate psychometric properties [101]. We measure stress with the German version of the ten-item Perceived

Stress Scale, which has demonstrated good reliability (Cronbach's α = 0.84) and validity [102]. Therein, stress is operationalized as the degree to which life is experienced as unpredictable, uncontrollable, and overloaded in the past months on a five-point Likert scale (*never* to *very often*). Somatic multimorbidity is measured using the self-administered Patient Health Questionnaire Somatic Symptom Scale (PHQ-15), which has good reliability (Cronbach's α = 0.8) and validity [103]. This questionnaire measures the presence and severity of somatic symptoms during the past 4 weeks on a three-point Likert scale (*not bothered at all* to *bothered a lot*). The items assess symptoms clusters which account for more than 90% of physical complaints reported in out-patient settings [103]. Lastly, the German version of the Modified Cumulative Illness Rating Scale provides physician-rated scores of multimorbidity. This scale has a good inter-rater agreement and concurrent and predictive validity. It measures the presence and severity multimorbidity over 14 organ systems on a five-point scale (*no problem* to *extremely severe problem*) [104].

Subjective measurements related to sleep Multiple sleep-related variables are measured to characterize the impact of sleep disorders in the population. The German version of the Pittsburgh Sleep Quality Index [105] is used to quantify subjective sleep disturbance. This 18 item scale assesses subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. It has adequate psychometric properties (Cronbach's α = 0.83) [106]. The corresponding global score with a cut-off value of ≥ 5 has been shown to distinguish good and poor sleepers [107]. We measure sleep reactivity, i.e., the degree to which an individual experiences disrupted sleep due to stress, with the Ford Insomnia Response to Stress Test [108, 109]. The nine-item self-report questionnaire is answered on a four-point Likert scale (*not very likely* to *very likely*) with higher total scores indicating a higher likelihood of stress-induced insomnia. The reliability (Cronbach's α = 0.80) and validity of the German version have been demonstrated [110]. Dysfunctional sleep-related thoughts and attitudes are related to the development and trajectory of sleep disorders [111]. The reliability and validity of the German short form of the dysfunctional beliefs and attitudes about sleep scale have recently been demonstrated (average Cronbach's α = 0.71) [112]. Sixteen items measure four domains (consequences, worry/helplessness, expectations, medication) on a ten-point Likert scale (*strongly disagree* to *strongly agree*). Excessive daytime sleepiness is associated with insomnia and depression [113, 114] as well as reduced quality of life and work performance [115]. We assess chronic daytime sleepiness using the German version of the Epworth Sleepiness Scale. This questionnaire has good reliability (Cronbach's α 0.83 in patients) and validity [116]. The likelihood of dozing off in eight daily situations (e.g., sitting and reading) is assessed on a four-point Likert scale (*would never doze* to *high chance of dozing*). Chronotype, i.e., peak alertness throughout the day, is associated with more severe depression, insomnia, and suicidality in patients with major depression. Furthermore, eveningness substantially increased the risk of non-remission independently of insomnia severity [117]. The Morningness-Eveningness Questionnaire assesses chronotype with 19 multiple-choice questions (four- or five-point scale) on sleep habits and propensity for performance throughout the day. The sum ranges from 16 to 86 and can be translated into chronotypes (< 42, evening type; 42–58, neither; > 58, morning type) [118]. Criterion validity has been established [119]. Validity and reliability (test-retest reliability > 0.96) have been confirmed for the German version [120].

Polysomnography (baseline and follow-up)

Polysomnography is considered the gold standard of sleep assessment [121]. However, one significant drawback of this method is the so-called *first-night effect*. This effect describes altered sleep patterns due to novel environments, disturbances by measurement equipment, a potential Hawthorne effect, or a combination thereof [122]. Such alterations typically represent worse sleep quality, e.g., reduced sleep efficiency, in the first compared to the second night [122]. Although this effect has been found in different patient groups, it is clearly attenuated in individuals with depression [123–125]. Moreover, polysomnographic measurements are expensive and performing multiple measurements is not always feasible. Several authors argue that data from the first night (i.e., baseline) should, therefore, be used in the analyses [123, 125]. In designs where baseline and follow-up data are collected, analysis of covariance (ANCOVA) has multiple advantages. Firstly, there is less potential for bias compared to the analysis of change (i.e., pre minus post) scores or follow-up data only. Secondly, ANCOVA has higher statistical power [126, 127].

Montage Polysomnography is performed with the SOMNOscreen™ plus RC (Somnomedics, Randersacker, Germany) using the following montage: one EEG channel (Fp2-A1, 512 Hz), two EOG channels (1 cm below and 1 cm lateral of the outer right canthus as well as 1 cm above and 1 cm lateral of the outer left outer canthus, 512 Hz), one EMG channel (Chin1-Chin2, 512 Hz), one ECG channel (modified lead II, 512 Hz), thoracic respiratory effort channel (inductance plethysmography belt, 32 Hz), finger photoplethysmography (non-dominant arm, 128 Hz),

body position (stored every 30 s), movement (32 Hz), and ambient light (stored every 30 s). Relevant skin areas are prepared with Nuprep (Weaver & Co., Aurora, CO, USA) before electrode placement to reduce skin impedance. Although this montage does not comply with AASM standards [128], the use of a single channel EEG, two EOG channels, and one EMG channel has been shown to have good validity when assessing sleep stages [129].

Analysis of polysomnography We apply low- and high-frequency filters according to AASM guidelines [128]. Oxygen desaturation index (ODI) is defined as the number of oxygen desaturations (≥ 4%) measured by photoplethysmography per hour of total sleep time [128]. We analyze polysomnography data visually in epochs of 30 s by two trained, independent, and blinded raters according to AASM guidelines [128]. If sleep efficiency differs by ≤ 5% between raters, we use the mean of each quantitative sleep parameter of both raters for analysis. If sleep efficiency differs by > 5% between raters, a consensus scoring is done by a third rater who is blinded against allocation and previous ratings. Inter-rater reliability (intraclass correlation) based on the scoring of the first two raters will be provided for the primary outcome. Sleep parameters are calculated with the proprietary DOMINO software (Somnomedics, Randersacker, Germany) (Table 2).

Sleep parameters can be grouped into three domains:

1. Sleep continuity: high sleep efficiency, low sleep onset latency, low wake after onset, low number of awakenings
2. Sleep depth: less stage 1 and 2 sleep, more stage 3 (i.e., slow wave) sleep
3. REM pressure: low REM latency, more REM sleep, (high REM-density)

***Nocturnal* autonomic cardiovascular modulation** Sleep hygiene recommendations include daily exercise. Two caveats of this recommendation are that exercise should be performed before 2 pm and that no strenuous exercise ought to be done close to bedtime. One reason for this recommendation is that exercise in the afternoon or evening might increase arousal and thereby prevent sleep [59]. However, evidence from numerous epidemiological, observational, and experimental studies have repeatedly failed to show such an adverse effect or have found that the opposite is true [54, 130]. The issue of nocturnal autonomic modulation following exercise is of central importance for three reasons. Firstly, arousal is integral to one of the most widely accepted etiological theories of insomnia [15, 16]. Secondly, heart rate variability (HRV), as a marker of autonomic arousal, has been proposed as a potential pathophysiological mechanism linking depressive disorders [131, 132] and insomnia [133] with cardiovascular disease. Thirdly, nocturnal blood pressure and nocturnal blood pressure dipping are of prognostic relevance for cardiovascular disease [134]. Therefore, sleep quality, as well as nocturnal autonomic activity, should be assessed when evaluating interventions in sleep research. Measurements of heart rate, HRV, and pulse transit time (and thereby calculated blood pressure) are collected to quantify the effect of exercise on parameters of autonomic cardiovascular arousal.

Table 2 Sleep parameters

Sleep parameter	Definition
Total recording time (TRT)	Time between the lights-off and lights-on markers (min)
Total sleep time (TST)	Time asleep (in any sleep stage) within TRT (min) TST = N1 + N2 + N3 + REM
Sleep onset latency (SOL)	Time between lights-off marker and first epoch of any sleep stage
Wake after sleep onset (WASO)	Time awake after first sleep episode (min) WASO = TRT - SL - TST
Number of awakenings (NA)	Number of wake periods of at least two epochs after sleep onset
Sleep efficiency (SE)	Percentage of sleep while in bed (%) SE = (TST / TRT) × 100
N1	Stage 1 (in minutes and % TST)
N2	Stage 2 (in minutes and % TST)
N3	Stage 3 (in minutes and % TST)
Light sleep	Stage 1 and 2 (in minutes and % TST)
NREM (non-REM) sleep	Stage 1–3 (in minutes and % TST)
REM	Rapid eye movement (in minutes and % TST)
REMLAT	Time between sleep onset and the occurrence of the first REM sleep epoch (min)
Stage shift index	Number of transitions between any wake or sleep stage/hours of sleep

We record the ECG while subjects are lying in bed. Patients were instructed to lie in the supine position and refrain from speaking as well as moving during the two short-term (i.e., 5-minute) recordings. No instructions concerning breathing were given. All ECG measurements were sampled at 512 Hz using modified lead II.

Three sections of HRV data are analyzed:

1. A short-term pre-sleep measurement with a duration of 5 min, beginning after lights off, is taken to quantify pre-sleep autonomic modulation. Measurements in which patients have fallen asleep are excluded from the analysis.
2. A nocturnal 6-h segment beginning after sleep onset. We choose this definition of the nocturnal HRV assessment for multiple reasons. According

to guidelines, durations of recordings have to be of equal length [135]. Nocturnal measurement segments of 4 or 6 h are frequently used in studies [136, 137]. In such trials, the starting point of the measurement period is usually defined by either sleep onset (identified by EEG or sleep diary) or a fixed time (e.g., 00:00). Since sleep onset is associated with increased parasympathetic modulation [138], we use sleep onset defined by polysomnography to mark the starting point of the segment to be analyzed. Using this starting point avoids potential bias which might be introduced by inter-individual differences in sleep onset latency and chronotype when using a fixed time. We chose a 6-h segment as it offers a more extended measurement period than 4 h. Moreover, 6 h is commonly considered the cut-off for objective short sleep duration [139, 140] and thus can be understood as a minimum sleep requirement for most individuals. Nocturnal HRV is dynamic, as non-REM sleep (primarily during the first half of the night) and REM sleep (primarily during the second half of the night) are characterized by parasympathetic and sympathetic predominance, respectively [138, 141]. We split the 6-h period into hourly segments, which allows the dynamic mentioned above to be partially captured.

3. A short-term post-sleep segment of 5 min beginning after the last awakening and before standing up to quantify post-sleep autonomic modulation. Patients are instructed to lie supine in bed after awakening for 5 min (using a timer). The post-sleep measurement has the advantage of limiting external factors which influence HRV.

The time- and frequency-domain measures which we calculate are described in Table 3. Low (LF) and high frequency (HF) power in normalized units (LFnu and HFnu) will not be reported. The rationale for this deviation from guidelines is that LFnu, HFnu, and LF/HF ratio have been shown to carry algebraically and therefore physiologically redundant information [142, 144]. Reporting of data collection, analysis, cleaning, and calculation will follow the GRAPH guidelines [145]. The percentage of beats identified as artifacts will be reported for both groups for each segment (median and inter-quartile range). Measurements with > 5% artifacts will be excluded from analysis.

An ongoing debate in the literature concerns the choice of method for spectral analysis. Fast Fourier transform (FFT) using Welch's periodogram and auto-regressive modeling (AR) seem to be the most frequently used methods for power spectral analysis [135, 143]. Another method to estimate power spectral density is the Lomb-Scargle periodogram (LSP) [146, 147]. LSP has numerous advantages when compared to FFT and AR. LSP is designed to estimate the power density spectrum directly from the unevenly sampled tachogram. AR and FFT, on the other hand, need to be interpolated and resampled to fulfill the prerequisite of evenly sampled data. Resampling leads to over- and under-estimation of LF and HF, respectively [148, 149]. FFT and AR require a

Table 3 HRV parameters

Method	Measure of variability	Calculation of variable	Physiological mechanism
Time-domain methods			
Statistical	RMSSD	Root mean square of successive differences of NN intervals	Short-term components of HRV, vagal modulation
	SDNN	Standard deviation of the of all NN intervals	Overall HRV, cyclic components responsible for HRV
	SDANN	Standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (only for nocturnal HRV)	Long-term components of HRV
Frequency domain methods			
Lomb-Scargle Periodogram and Fast Fourier transformation	TP	Total power: power density spectrum in the frequency range of 0.00001 to 0.4 Hz [ms^2]	Overall HRV
	LF	Low-frequency power: power density spectrum in the frequency range of 0.04 to 0.15 Hz [ms^2]	Sympathetic and vagal activity, baroreflex activity (vasomotor tone)
	HF	High-frequency power: power density spectrum in the frequency range of 0.15 to 0.40 Hz [ms^2]	Vagal modulation
	LF/HF	Ratio LF [ms^2]/HF [ms^2]	Sympathetic and vagal modulation

Calculations are based on [135, 142]. Descriptions of physiological mechanisms are based on [142, 143]

trade-off between frequency resolution and time resolution (statistical stability) when choosing window length [150] and model order [151], respectively. In contrast, LSP makes no assumptions of models. Investigations have shown that LSP is more accurate [152–154], is less noisy [154], has higher reliability [155], and is more sensitive to physiological changes [155–157] when compared to FFT. Consequently, multiple authors have suggested LSP as the method of choice for spectrum analysis of HRV [152, 158]. For these reasons, we estimate power spectral density using LSP smoothed with a moving average filter (width 0.02 Hz) in this trial. To enable comparison with other studies, we also calculate Welch's FFT and will report it as a sensitivity analysis.

We perform ECG pre-processing and HRV analysis using Kubios HRV (University of Eastern Finland, Kuopio, Finland) [159]. This software has been shown to have perfect intra-class correlation coefficients (ICC = 1.000) across HRV variables measured during different postures when compared to two other software [120]. QRS detection is based on the Pan-Tompkins algorithm [160], including bandpass filtering. Beat detection is visually inspected. Erroneously detected RR fiducial points are corrected by manual editing of R-wave. Artifacts are identified using the automatic artifact correction algorithm [161]. This algorithm has been shown to detect ectopic beats with an accuracy of 97%. Ectopic beats are replaced by phantom beats using cubic spline interpolated RR values. Correction of aberrant RR intervals using cubic spline interpolation has been shown to perform as well as other correction methods for frequency analysis [162]. Detrending, i.e., removal of slow-trend and non-linear trend components is performed using the smoothness priors approach [163] with $\lambda = 500$ and $f_c = 0.035$ Hz (thus not affecting the lower band of LF). Frequency-domain variables estimated by LSP are based on de-trended RR series. Frequency-domain variables estimated by FFT with Welch's periodogram are based on de-trended as well as interpolated (i.e., resampled) RR series. We employ the following parameters for power spectral density estimation using FFT. RR series are resampled to obtain an evenly sampled time series using a cubic spline interpolation with a rate of 4 Hz. A Hann window with a width of 60 s and 50% overlap is used (corresponding to 240 samples). These window parameters are chosen to balance the requirement of stationarity and frequency resolution resulting in an average of 9 and 119 FFT spectra for 5 min and hourly segments, respectively, with a frequency resolution of 0.025 Hz. Singh et al. [150] have shown that these approximate parameters produce a good spectral estimate (smooth with clear peaks).

Pulse transit time is calculated using ECG and pulse waveform from photoplethysmography. Blood pressure (BP) is calculated using the pulse transit time. This method has been validated [164] according to the European Society of Hypertension International Protocol (ESH-IP) revision 2010 criteria [165]. Accordingly, we perform a single initial calibration measurement (manual cuff-based method, contralateral arm of photoplethysmography, sitting position). Two significant advantages of this method are the continuous measurement of BP and elimination of cuff inflations. The latter is poorly tolerated by patients, causes awakenings, and may affect the validity of BP measurements [166]. BP levels differ between non-REM and REM sleep [167]. Therefore, mean systolic, mean diastolic, and mean arterial pressures will be reported separately for total sleep time, non-REM sleep, and REM sleep.

Subjective sleep-related measurements

Subjective pre-sleep arousal has been shown to be increased in primary insomnia [168] and seems to partially mediate the relationship between depressive symptoms and daytime fatigue [169]. We use the German version of the Pre-Sleep Arousal Scale to assess cognitive and somatic pre-sleep arousal. Eight and seven items load onto the factors somatic (Cronbach's $\alpha = 0.80$) and cognitive (Cronbach's $\alpha = 0.94$) arousal, respectively [170]. Items are scored on a five-point Likert scale (*not at all* to *extremely*) and summed up for each factor separately.

We measure subjective sleep quality of the baseline and post-intervention night using the revised *Schlaffragebogen A*, as recommended by guidelines [171]. Twenty-five items load onto five factors: sleep quality, recuperation after sleep, calmness before sleep, exhaustion before sleep, and psychosomatic symptoms during sleep. Internal consistency, factor structure, and validity have been demonstrated in numerous populations [172].

The clinical relevance of excessive daytime sleepiness is highlighted above (cf. rationale for ESS questionnaire). State sleepiness is recorded four times (0800, 1200, 1600, 2000 h) on the day after the experimental condition to gauge the effects on daytime somnolence. The Stanford Sleepiness Scale is a single item questionnaire assessing the degree of momentary sleepiness on a seven-point scale [173]. Adequate psychometric properties have been demonstrated [174].

Expectancy and credibility

Insomnia treatment guidelines stress the importance of contextual factors such as patient preference and satisfaction when choosing the most suitable therapy [88, 175]. Credibility can increase expectancy [176]. The latter has been shown to influence outcomes in depression and other disorders [177]. Since patients cannot be blinded in exercise studies, it is especially important to consider expectancy. We assess credibility and expectancy on day three (i.e., before randomization) using two items (adapted

from [178, 179]): "At this point, how logical does the therapy offered to you seem?", "At this point, how successfully do you think this treatment will be in reducing your insomnia symptoms?". Patients rate these items on a four-point Likert scale (*not at all* to *very*).

Randomization and blinding

A non-deterministic minimization algorithm is used to assign interventions. Allocation to intervention or control group is done using the open source software for online minimization (Oxford Minimization and Randomization, OxMaR) [180]. All necessary data for minimization is collected using surveys integrated into the eCRF. The required data are entered in the web-based randomization software by the study nurses. Upon confirmation that the data are correct, the study participant is allocated to a group, the allocation is saved in a central database, and an e-mail containing the allocation is sent to the PI, the study coordinator, and to the person submitting the participant. Allocation concealment consists of four aspects: (1) requesting randomization after baseline measurement, (2) use of a random element, (3) requesting allocation for participants by two different study nurses, and (4) not disclosing full details of minimization to study nurses in accordance with the SPIRIT guideline [67]. We will publish a detailed description of the minimization scheme with the results of the trial.

It is impossible to blind participants in exercise trials. However, we prevent detection bias though objective sleep measures which are assessed by two blinded and independent assessors. Blinding is ensured by replacing the subject ID with a second unique ID number. The list matching these IDs is not accessible to the raters.

Intervention and control condition

Aerobic exercise (intervention) Patients allocated to the intervention group perform a single bout of supervised aerobic exercise. The starting time is approximately 1645 h. The exercise mode is a bicycle ergometer (ergoselect 200, Ergoline, Bitz, Germany). After a warm-up period of 5 min, during which the intensity is gradually increased, patients maintain an intensity of 80% of the individual anaerobic threshold for 30 min. The intensity level is chosen based on clinical experience that this corresponds to an approximate rate of perceived exertion of 13 (on a scale from 6 to 20) in this population. The duration of exercise corresponds to physical activity recommendations [181].

Control condition At the same time as individuals performing the exercise intervention, individuals allocated to the control group are placed in a room which is comparable to that of the exercise group concerning light, temperature, and absence of music. The control group is asked to remain seated and read magazines.

The rules and schedules of the inpatient rehabilitation clinic (e.g., timing of meals, consumption of multimedia, and alcohol) limit the variability of many behavioral aspects which could influence sleep. Occasional smokers are asked to refrain from smoking after dinner on the days of polysomnographic assessment. Chronic smokers are not asked to abstain from smoking as this might be an additional stressor.

Adherence and other outcomes of interest We assess the implementation of the intervention with continuous measurement of Watts and heart rate using a Polar® H7 chest strap (Polar OY, Finland). We measure heart rate throughout the intervention period, including 3 min post-exercise. We measure perceived exertion using the Borg scale (6–20) [93]. All subjects complete a questionnaire on their current mood immediately before and at the end of the control condition as well as the exercise intervention. The *Befindlichkeitsskala* has adequate psychometric properties [182] and is considerably more economical than other comparable measures [183]. The questionnaire consists of 40 items on a five-point Likert scale (*not at all* to *very much*). Items load onto eight subscales (with five items each): activity (Cronbach's $\alpha = 0.82$), elation (Cronbach's $\alpha = 0.81$), contemplation (Cronbach's $\alpha = 0.70$), calmness (Cronbach's $\alpha = 0.78$), fatigue (Cronbach's $\alpha = 0.88$), depression (Cronbach's $\alpha = 0.80$), anger (Cronbach's $\alpha = 0.86$), and excitement (Cronbach's $\alpha = 0.73$) [182]. Contamination through any or additional physical activity (depending on the allocation) is assessed using a wrist-worn accelerometer (on non-dominant hand) on the days prior to and after the sleep assessments. The wrist-worn accelerometer vivofit®2 (Garmin, Schaffhausen, Switzerland) validly assesses steps in various walking conditions [184]. Although adequate blinding cannot be achieved by design in exercise studies, this allows for a partial assessment of performance bias.

Concomitant, ancillary, and post-trial care The trial takes place in the first 5 days of the patient's psychosomatic in-patient rehabilitation. The rehabilitation programme entails different therapies, including exercise therapy. Patients included in the study are asked to refrain from exercise except as defined by the protocol on the days of testing. Patients are explicitly made aware of this aspect before enrollment. Ancillary and post-trial care is provided throughout the in-patient rehabilitation program, i.e., on average for 4 weeks after completion of the study.

Adverse events We assess adverse events through a questionnaire. We ask patients in both groups whether they experience adverse effects on a five-point Likert scale (*not at all* to *very*) using the following categories immediately after the intervention and the following morning:

- Pain (if yes, location)
- Dizziness
- Cardiovascular symptoms (e.g., angina symptoms, cyanosis, pallor)
- Respiratory symptoms (e.g., wheezing)
- Nausea
- Falls (yes or no)
- Other (to be described)

Unplanned termination of participants and the reasons thereof (if participant proactively gives one) will also be reported.

Data management

Data collection

We use castor electronic data capture software for data collection and data management [185]. This software complies with Good Clinical Practice guidelines and the European Data Protection Directive. A unique numeric subject ID is assigned to each participant to conceal the identity of participants in the database. The file which links the numeric subject ID to the participant information is kept in a password-protected folder in an encrypted digital file and on paper in a locked cabinet. These digital and paper files are exclusively stored at the study site. Only the study nurses, the study coordinator, and the principal investigator have access to this information. Regulatory agencies (i.e., ethics committee) will also be granted access upon request. Patient data are collected using electronic case report forms (eCRF). Range and dependency checks are implemented into the eCRF and completeness checks of data for each participant are performed during the trial. The eCRF can be found in Additional file 3. All study personnel have been trained in measurement procedures and data collection according to the case report form using standard operating procedures to ensure standardized data collection. Data from the polysomnography are uploaded to the CASTOR platform using the subject ID to match data.

Security, storage, and access

Study nurses, the study coordinator, the principal investigator, and monitors can access the password-protected database. The principal investigator and study coordinator define user accounts and user rights according to their responsibilities, e.g., authorization for data changes. All changes in the eCRF are saved in data trails, audit trials, and edit trails, (including reasons for changes). The data are stored for 15 years. The study coordinator and principal investigator will have full access to the trial data.

Data monitoring and audits

Due to the risk stratification of this trial, the need for a data-monitoring committee is waived. Central data monitoring is performed using the built-in modules of the CASTOR software. No interim analyses are planned. Monitoring of regulatory files, study processes, and data is conducted in four visits: before enrollment of the first patient, after enrollment of the first patient, after enrollment of 50% of patients, and after last patient last visit. Monitoring is done by the Clinical Trial Unit, Basel, Switzerland (i.e., an organization independent from the investigator and sponsor).

Statistical methods

Sample size calculation

The theoretical rationale for the analysis of the primary outcome, using an ANCOVA model, is outlined above (see the "Polysomnography (baseline and follow-up)" section). Furthermore, minimization necessitates adjustment for minimization factors [186]. Sample size calculation was performed according to the procedure defined by Borm et al. [187]. The allocation ratio is 1:1. The expected treatment effect is based on the work of Passos et al. [63], who found a standardized mean difference in sleep efficiency of 0.53. The estimate is based on this publication because it is the only one known to the authors which (1) evaluated the *acute* effect of (2) a similar intervention (i.e., moderate aerobic exercise) (3) in individuals with sleep disorders. Due to the well-documented ceiling and floor effects [188], meta-analyses concerning predominantly healthy individuals (explicitly excluding individuals with mental disorders) [54] are of no use. Meta-analyses including individuals with sleep complaints are limited to the analysis of the *chronic* effects of exercise on sleep [55, 189]. With a power of 0.8 and a two-sided alpha of 0.05, 57 subjects would be required for each group using a *t*-test. According to the method of Borm et al., this sample size can be multiplied by a 'design factor' of $(1 - \rho^2)$, where ρ is the correlation coefficient between baseline and follow-up outcome [187]. Despite contacting other researchers, the authors are not aware of any previous study which have analyzed this aspect. Hence, we need to make an estimate. Recommended values for imputation of ρ vary between 0.5 (if variances are equal at pre- and post-measurements, ρ is at least 0.5) and 0.7 [190, 191]. We use a conservative estimate and let $\rho = 0.5$. This leads to a design factor of 0.75 ($1 - 0.5^2 = 0.75$). Hence, the sample size needed per group is 43 (57 ×

0.75 = 42.75). Due to the short-term nature of this study, we expect approximately half the dropout rate of trials investigating the chronic effects of exercise in patients with depression [192]. Thus, we anticipate 7% dropouts. Therefore, the total sample size is 92 (2 × 43 × 1.07 = 92).

Analysis of the primary outcome

The main aim of this trial is to analyze the acute effect of aerobic exercise on the subsequent night's sleep efficiency measured by polysomnography. To this end, we will compute a one-way ANCOVA with baseline sleep efficiency and minimization factors as covariates, intervention as the independent variable, and post-exercise sleep efficiency as the dependent variable. Clinical significance will be determined using the criteria defined in the American Academy of Sleep Medicine Clinical Practice guideline for the Pharmacological Treatment of Chronic Insomnia in adults. Thereby, an absolute change in sleep efficiency of ≥ 5% is deemed clinically relevant. We define responders as individuals who have an increase in sleep efficiency of ≥ 5% from baseline to post-intervention. We will report the number, the proportion, and the odds ratio of responders as well as the number needed to treat. In order to reduce attrition bias to a minimum, all analyses will follow the intention-to-treat framework.

Sensitivity analyses for the primary outcome will be performed to gauge the influence of several factors: outliers (defined as < Quartile 1 − 1.5 × Interquartile range; > Quartile 3 + 1.5 × Interquartile range), per-protocol analysis (to reflect optimal adherence to treatment), missing data (analysis of complete data only), excluding minimization factors (age, sex, PHQ-9 score, and Pittsburgh Sleep Quality Index score), chronotypes, smoking status, and use of beta-blockers. We will report all results of sensitivity analyses. We will replace missing data using multiple imputation with the *mi* package in R [193]. The quantity of missing data will be reported.

Analysis of secondary outcomes

Secondary outcomes will also be analyzed using ANCOVA models when variables have been assessed at baseline and follow-up. Hourly segments of nocturnal HRV will be analyzed using a linear mixed model with subject as random effect, adjusting for baseline and minimization factors. Acute daytime sleepiness will be assessed using repeated measures ANOVA with Benjamini-Hochberg [194] corrected post hoc paired sample *t*-tests. Measurements where only post-intervention group-comparisons are possible will be analyzed using *t*-tests. The threshold for statistical significance is set at $p < 0.05$. The authors point out that the secondary analyses are not adjusted for multiple testing and are of exploratory nature.

Ethics and dissemination

Ethics approval

The Ethics Committee East Switzerland, St. Gallen, Switzerland, has approved the study (EKOS 18/089). We registered the trial with the ClinicalTrials.gov database (NCT03673397) on September 17, 2018. No protocol amendments have been made. Approval for any potential future amendments will be obtained from the local ethics committee.

Dissemination policy

We will disseminate trial results to all stakeholders, e.g., participants (if they choose to receive these at enrollment), physicians, and study nurses. Results will be published in a peer-reviewed journal and presented at conferences as well as invited talks. Authorship on peer-reviewed publications will be based on contributions toward design, fundraising, data collection, analysis, and manuscript preparation. De-identified (i.e., coded) individual participant data that underlie the results of published articles, including data dictionaries, will be available upon request under the creative commons license CC-BY. Requests will only be granted for use in individual participant data meta-analysis which has been approved by an independent review committee. Exceptions to these rules are reserved within the context of peer-reviewed publications, provided that data integrity remains intact. Data will be provided upon request immediately after publication of peer-reviewed articles with no end date. Requests should be sent to the e-mail address detailed in the following Dataverse repository (https://doi.org/10.7910/DVN/WASN36).

Discussion

The goal of this two-arm parallel group, individually randomized, single-blind, controlled trial is to assess the superiority of an acute bout of aerobic exercise compared to no intervention in improving the subsequent night's sleep efficiency in patients with a primary diagnosis of depression. To the knowledge of the authors, this is the first trial to investigate the acute effects of exercise on sleep in this population.

The main strength of this study is the objective measurement of sleep. Moreover, multiple secondary outcomes were carefully selected to provide clinicians, patients, and policy makers with a comprehensive picture of the effects this intervention may have. Explicit inclusion of patients with comorbidities should enhance the external validity of this study. Accordingly, we provide extensive baseline characterization.

The main limitation of this trial is the restricted polysomnographic EEG montage. More detailed analyses, such as spectral EEG analysis, will therefore not be possible. Extensive discussions in our research group

resulted in an explicit trade-off between the patients' discomfort (number of EEG channels) and feasibility of recruitment. The restricted EEG montage will help to recruit the necessary number of patients in an adequate period in this clinical setting. The pre-selection of patients who are treated in this rehabilitation clinic might pose a further limitation. Extensive baseline characterization will help readers identify limits to external validity. Patients cannot be blinded against allocation in exercise trials. We try to overcome this limitation through various measures (see above).

There is compelling evidence for the effectiveness of various therapies for both insomnia and depression. Nevertheless, many of these therapies have shortcomings. Development of further therapeutic options, which can be administered in addition to these therapies, are therefore needed. Current literature suggests that acute aerobic exercise might improve both depression and insomnia. Although chronic aerobic exercise is included in sleep hygiene recommendations, there is uncertainty concerning the acute effects of aerobic exercise on sleep in patients with depression. This trial aims to close this gap in the literature as well as to help the increasing number of patients with depression.

Trial status

We registered this trial on September 17, 2018, in the ClinicalTrials.gov database (NCT03673397). All items of the World Health Organization Trial Registration Data Set can be found in the ClinicalTrials.gov registration. This is the first version of the protocol, i.e., we have made no amendments. Recruitment began on September 24, 2018. Recruitment is expected to be completed by October 2019.

Additional files

Additional file 1: SPIRIT checklist. (PDF 171 kb)
Additional file 2: Original consent form in German. (PDF 561 kb)
Additional file 3: Electronic case report form (eCRF). (PDF 504 kb)

Abbreviations

ANCOVA: Analysis of covariance; AR: Autoregressive modeling; BMI: Body mass index; BP: Blood pressure; CBT-I: Cognitive behavioral therapy for insomnia; ECG: Electrocardiogram; eCRF: Electronic case report form; EEG: Electroencephalogram; EOG: Electrooculogram; FFT: Fast Fourier transform; HF: High frequency power; HRV: Heart rate variability; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th revision; LF: Low frequency power; LSP: Lomb-Scargle periodogram; N1–N3: Stage 1–3 sleep; NA: Number of awakenings; ODI: Oxygen desaturation index; PHQ: Patient Health Questionnaire; REM: Rapid eye movement; SE: Sleep efficiency; SOL: Sleep onset latency; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT); TRT: Total recording time; TST: Total sleep time; WASO: Wake after sleep onset

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Not applicable.

Authors' contributions

GB, DS, HP, TZS, MG, RvK, and AST contributed to the design, revised the manuscript, and approved the final manuscript. GB conceived the trial design, drafted the manuscript, registered the protocol with ClinicalTrials.gov, and managed the overall project.

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Availability of data and materials

The dataset supporting the conclusions of this article is available in the Dataverse repository (https://doi.org/10.7910/DVN/WASN36). De-identified (i.e., coded) individual participant data that underlie the results of published articles, including data dictionaries, will be available upon request under the creative commons license CC-BY. Requests will only be granted for use in individual participant data meta-analysis which has been approved by an independent review committee. Exceptions to these rules are reserved within the context of peer-reviewed publications, provided that data integrity remains intact. Data will be provided upon request immediately after publication of peer-reviewed articles with no end date. Requests should be sent to the e-mail address detailed in the Dataverse repository mentioned above.

Ethics approval and consent to participate

The Ethics Committee East Switzerland, St. Gallen, Switzerland, has approved the study (EKOS 18/089).

Consent for publication

Not applicable.

Competing interests

Gavin Brupbacher is funded through an industry sponsored PhD, provided by OBERWAID AG, St. Gallen, Switzerland. Dr. Doris Straus and Dr. Hildburg Porschke are employed by OBERWAID AG. Arno Schmidt-Trucksäss and Roland von Känel are on the scientific advisory board of the Oberwaid AG. All other authors declare no competing interests.

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Publisher's Note

Chapter 6

Publication 4: The acute effects of aerobic exercise on sleep in patients with unipolar depression: a randomized controlled trial

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ORIGINAL ARTICLE

The acute effects of aerobic exercise on sleep in patients with unipolar depression: a randomized controlled trial

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Abstract

Study Objectives: Insomnia increases the risk of negative disease trajectory, relapse, and suicide in patients with depression. We aimed at investigating the effects of a single bout of aerobic exercise, performed after 02:00 pm, on the subsequent night's sleep in patients with depression.

Methods: The study was designed as a two-arm parallel-group, randomized, outcome assessor-blinded, controlled, superiority trial. Patients between 18 and 65 years of age with a primary diagnosis of unipolar depression were included. The intervention was a single 30-minute bout of moderate aerobic exercise. The control group sat and read for 30 minutes. The primary outcome was sleep efficiency measured by polysomnography. Secondary outcomes were other polysomnographic variables, subjective sleep quality, daytime sleepiness, mood states, and adverse events.

Results: Ninety-two patients were randomized to the exercise ($N = 46$) or control group ($N = 46$). There were no clinically relevant differences at baseline. Intent-to-treat analysis ANCOVA of follow-up sleep efficiency, adjusted for baseline levels and minimization factors, did not detect a significant effect of the allocation ($\beta = -0.93$, $p = 0.59$). There was no evidence for significant differences between both groups in any other objective or subjective sleep outcomes, daytime sleepiness, or adverse events. The intervention had an immediate positive effect on mood states, including depressiveness ($\beta = -0.40$, $p = 0.003$).

Conclusions: This is the first trial to study the effects of a single bout of aerobic exercise on sleep in patients with depression to the best of our knowledge. Aerobic exercise had no effect on sleep efficiency but had a strong beneficial effect on mood and did not increase adverse outcomes. These results add to the growing body of evidence that, contrary to sleep hygiene recommendations, exercise after 02:00 pm is not detrimental for sleep.

Clinical Trial Registration: Clinicaltrials.gov, https://clinicaltrials.gov/ct2/show/NCT03673397. Protocol registered on September 17, 2018.

Statement of Significance

Insomnia is a core symptom of unipolar depression. This is the first trial to study the acute effects of aerobic exercise on sleep in patients with depression to the best of our knowledge. We found no evidence for an effect of allocation on sleep-related variables or adverse effects. However, a single session of moderate aerobic exercise substantially improved mood states.

Key words: depression; mood; exercise; sleep; polysomnography; randomized controlled trial

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Introduction

Insomnia is a core symptom of unipolar depression, which critically predicts depression onset, trajectory, and recurrence. Insomnia is defined as having difficulties initiating or maintaining sleep, early morning awakening and is often accompanied by daytime impairments [1]. Meta-analysis has shown that insomnia more than doubles the risk for depression [2]. This risk might be mainly driven by difficulties initiating sleep, as was suggested by a recent network outcome analysis [3]. Epidemiological studies have found insomnia prevalence rates of up to 90% in patients with depression [4]. Longitudinal studies have repeatedly shown a bidirectional link between insomnia and depression [5]. Insomnia symptoms negatively affect the disease trajectory [6]. It reduces the responsiveness to psychotherapy [7], pharmacotherapy, or a combination of these [8, 9]. It also seems to increase the risk of developing treatment-resistant depression [10], suicidal behavior [11], as well as myocardial infarction [12]. Sleep complaints are one of the most common symptoms after remission [13]. Residual insomnia is problematic because insomnia is a prodromal symptom [14], thereby increasing the risk for depression relapse [15]. There is a need to develop additional treatments for insomnia in patients with depression, considering the evidence presented above.

Moderate aerobic exercise might be a viable candidate as an adjuvant therapy for insomnia in patients with depression. Aerobic exercise is a rhythmic activity that involves large muscle groups and that primarily uses aerobic energy-producing systems. Moderate aerobic exercise refers to intensities of 55%–69% maximal heart rate, 40%–59% heart rate reserve, or 11–13 rate of perceived exertion [16]. Regular moderate aerobic exercise has positive effects on subjective sleep quality in patients with depression, as we have demonstrated in a recent network meta-analysis [17]. These effects are particularly strong when aerobic exercise is combined with treatment as usual. Regular moderate aerobic exercise also improves symptoms of depression [18]. Furthermore, chronic aerobic exercise improves cardiorespiratory fitness in patients with depression [19]. The effect on fitness is pertinent because depression increases the risk of coronary heart disease and myocardial infarction [20]. Current general sleep hygiene guidelines recommend regular exercise before 02:00 pm [21]. The authors of this guideline argue that vigorous exercise before bedtime causes the release of endorphins which can delay the onset of sleep [21]. This caveat on timing severely limits the feasibility of exercise interventions. Moreover, epidemiological data [22] and meta-analysis of randomized controlled trials in healthy individuals [23] have shown that there is no adverse effect of an exercise bout after 02:00 pm on sleep. This reflects the lack of evidence concerning the *acute* effects of moderate exercise on sleep, especially in patients with depression.

The primary goal of this trial was, therefore, to investigate the effects of a single bout of moderate aerobic exercise on the subsequent night's sleep efficiency in patients with depression. For the duration of the exercise bout, we chose 30 min, corresponding to the recommendation of the American College of Sports Medicine and the American Heart Association for daily physical activity with beneficial health effects [24]. Secondary goals were to investigate the intervention's effect on other polysomnographic outcomes, adverse outcomes, daytime sleepiness, and mood. We hypothesized that the intervention improves (1) sleep efficiency, (2) sleep continuity, (3) sleep architecture, (4) subjective sleep quality, (5) daytime sleepiness, and (6) mood. We expected no evidence for an effect on the frequency and the severity of adverse events as an exploratory outcome.

Methods

Trial design

This was a two-arm parallel-group, randomized, outcome assessor-blinded, controlled, superiority trial. The trial took place in the psychosomatic in-patient rehabilitation unit of the OBERWAID AG, a rehabilitation clinic in St. Gallen, Switzerland. The Ethics Committee East Switzerland, St. Gallen, Switzerland, approved the study protocol (EKOS 18/089). We prospectively registered this trial in the clinicaltrial.gov registry on September 17, 2018 (NCT03673397). A detailed study protocol that clearly states the study's rationale is available [25]. There were no amendments and no deviations from the protocol. This report follows the CONSORT guideline for randomized controlled trials [26]. The data underlying this article is available in the Harvard Dataverse at https://doi.org/10.7910/DVN/WASN36 and will be shared at reasonable request to the corresponding author.

Procedure and Assessments

Screening

Patients admitted to the in-patient psychosomatic rehabilitation unit of the OBERWAID clinic were screened for inclusion. The trial took place in the first 5 days of the patient's psychosomatic in-patient rehabilitation, see Figure 1. The first author or another representative of the OBERWAID AG obtained written informed consent from participants. Eligibility criteria are listed in Table 1. We provide a detailed rationale for the inclusion and exclusion criteria in the study protocol [25].

After providing informed consent, we formally screened patients. The screening included a consultation with an experienced psychiatrist and a full history and medical examination by an experienced internist. Patients with undiagnosed sleep apnea were excluded according to the baseline polysomnography.

Graded exercise testing

Patients fulfilling all eligibility criteria assessed thus far (sleep apnea criterion is determined later by polysomnography, see Figure 1) performed sub-maximal graded exercise testing on a bicycle ergometer (ergoselect 200, Ergoline, Bitz, Germany). We determined the anaerobic threshold according to the method of Dickhuth et al. [27] using a specialized software program (Ergonizer, Freiburg, Germany). A detailed description of the graded exercise testing can be found in the study protocol [25].

Patient characterization

We administered multiple questionnaires to characterize patients at baseline. We assessed somatic multimorbidity with the Patient Health Questionnaire Somatic Symptom Scale (PHQ-15) [28] and the Modified Cumulative Illness Rating Scale (CIRS) [29]. The PHQ-15 is a self-administered questionnaire with 15-items. It measures the severity of somatic symptoms

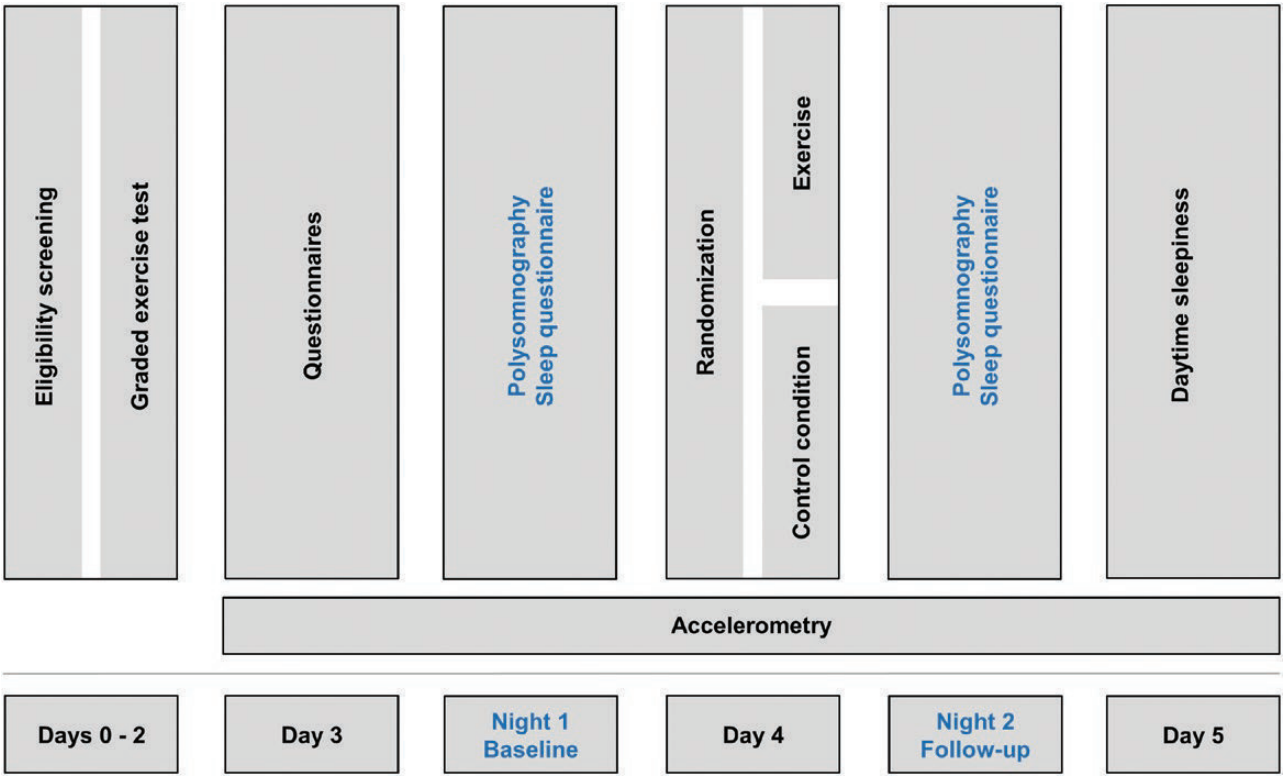

Figure 1. Trial design.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
• ≥18 and ≤65 years old
• Primary diagnosis of depression (F32, F33) without psychotic episode according to ICD-10
Exclusion criteria
• Regular use of hypnotic agents* (patients are included if no hypnotic agents were taken 2 weeks before study participation)
• Factors precluding exercise testing or training†
• Use of beta-blockers (except Carvedilol & Nebivolol)
• Use of opioids
• History of epilepsy
• Restless legs syndrome defined by ≥7 points on the Restless Legs Screening Questionnaire [35]
• Moderate or severe sleep apnea defined by an oxygen desaturation index (using 4% criterion) ≥ 15 in the baseline polysomnography
• Morbid adiposity with BMI > 40

*Hypnotic agents are defined as follows: orexin receptor agonists, benzodiazepine receptor agonists, sedating antidepressants, neuroleptics, benzodiazepines, melatonin agonists, heterocyclics, anticonvulsants, over the counter sleep aids (sedating antihistamines, melatonin L-tryptophan, valerian), and cannabinoids.
†Absolute and relative contraindications are based on ACSM's Guidelines for Exercise Testing and Prescription.
ICD-10, International classification of diseases, version 10; BMI, body mass index.

(e.g. back pain) within the previous 4 weeks on a three-point Likert scale (*0 = not bothered at all to 2 = bothered a lot*). The symptoms in this questionnaire account for more than 90% of physical complaints reported in outpatient settings and its validity has been demonstrated [28]. The CIRS provides physician-rated scores of multimorbidity. It measures the severity of symptoms over 14 organ systems (e.g. heart) on a five-point scale (*0 = no problem to 4 = extremely severe problem*). Inter-rater agreement and validity have been demonstrated [29]. We measured depressive symptom severity with the Patient Health Questionnaire-9 (PHQ-9) [30]. The nine symptom items (e.g. "Feeling down, depressed, or hopeless") are scored on a four-point Likert scale (*0 = not at all to 3 = nearly every day*). The psychometric properties, including the validity of the cutoffs from mild to severe depression, have been demonstrated [30]. Anxiety was assessed using the Hospital Anxiety and Depression Scale (HADS) [31]. This questionnaire measures anxiety with seven items (e.g. *"I get sudden feelings of panic"*), each on a four-point Likert scale (e.g. *0 = not at all to 3 = most of the time*). Psychometric properties, including diagnostic test accuracy, have been demonstrated [31, 32]. Stress was assessed with the Perceived Stress Scale [33]. This questionnaire operationalizes stress as the degree to which life is experienced as unpredictable, uncontrollable, and overloaded in the past month. The ten items (e.g. *"In the last month, how often have you felt nervous and stressed?"*) are scored on a five-point Likert scale (*0 = never to 4 = very often*). The psychometric properties have been demonstrated [33]. Sleep reactivity was assessed with the Ford Insomnia Response to Stress Test

[34, 35]. The nine items of this self-report questionnaire assess the likelihood of sleep disturbances in response to stressful situations (e.g. "*How likely is it for you to have difficulty sleeping after an argument*") on a four-point Likert scale (*1 = not very likely* to *4 = very likely*). Reliability and validity have been demonstrated [36]. Dysfunctional sleep-related thoughts and attitudes were assessed with the Short form of the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS) [37]. The sixteen items (e.g. "*I am worried that I may lose control over my ability to sleep.*") are rated on a Likert scale (*0 = strongly disagree* to *10 = strongly agree*). The reliability and validity of this questionnaire have been demonstrated [37]. Chronotype was assessed using the Morningness-Eveningness Questionnaire [38]. The 19 multiple-choice questions (four- or five-point scale) assess sleep habits and propensity for performance throughout the day. The sum score (range: 16 to 86) can be translated into chronotype (<42, evening type; 42–58, neither; >58, morning type). Adequate psychometric properties have been demonstrated [39, 40]. We measured chronic daytime sleepiness using the Epworth Sleepiness Scale [41]. The likelihood of dozing off in eight daily situations (e.g. watching television) is assessed on a four-point Likert scale (*0 = would never doze* to *3 = high chance of dozing*). The reliability and validity have been demonstrated [42]. Subjective sleep disturbance was measured with the Pittsburgh Sleep Quality Index [43, 44]. This 18 item scale assesses subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum score with a cutoff value of ≥5 has been shown to distinguish good and poor sleepers [45].

Since patients cannot be blinded in exercise trials and considering the importance of patient preference and satisfaction [46, 47], we also assessed credibility and expectancy on day three (i.e. before randomization) using two items (adapted from [48, 49]): "At this point, how logical does the therapy offered to you seem?", "At this point, how successfully do you think this treatment will be in reducing your insomnia symptoms?." Patients rated the credibility and expectancy items on a four-point Likert scale (*1 = not at all* to *4 = very*).

Baseline assessments

We assessed multiple objective and subjective sleep outcomes at baseline. We performed the baseline polysomnography on the night before the intervention to exclude patients with at least moderate sleep apnea (oxygen desaturation index ≥ 15) and assess potential first-night effects. We recorded polysomnographic data with the SOMNOscreen™ plus RC (Somnomedics, Randersacker, Germany) using the following montage: one EEG channel (Fp2-A1, 512 Hz), two EOG channels (512 Hz), one EMG channel, (512 Hz), one ECG channel (modified lead II, 512 Hz), thoracic respiratory effort channel (inductance plethysmography belt, 32 Hz), finger photoplethysmography (nondominant arm, 128 Hz), body position (stored every 30 s), movement (32 Hz), and ambient light (stored every 30 s). The validity of this montage for the assessment of sleep stages has previously been demonstrated [50]. Polysomnography recordings were scored independently by two trained scorers according to the American Association of Sleep Medicine guidelines [51]. All polysomnographic variables were calculated according to the American Association of Sleep Medicine guidelines [51]. Both scorers have demonstrated good agreement with the gold standard ratings in the AASM inter-scorer program [52]. Their average agreement with the gold standard was 88% and 84%, respectively, which is above average [53]. Scorers were blinded against allocation, time points, and each other's ratings. The subjective sleep quality of the baseline night was measured upon awakening with the revised *Schlaffragebogen A* [54], a German sleep questionnaire recommended by guidelines [55]. This self-report questionnaire contains 25 items that load onto five factors: sleep quality, recuperation after sleep, calmness before sleep, exhaustion before sleep, and nocturnal psychosomatic symptoms. Internal consistency, factor structure, and validity have been demonstrated [54].

Randomization

Once eligibility was confirmed by baseline polysomnography, patients were randomly allocated to one of both groups using minimization (see Figure 1). We used a nondeterministic unweighted minimization algorithm [56] with a random element of 0.8. The allocation ratio was 1:1. We used minimization to increase the probability of balanced groups across the following predictive factors: sex, age, depression severity (PHQ-9 score), and subjective sleep quality (PSQI score). Allocation concealment consisted of four aspects: (1) requesting randomization after baseline measurement, (2) using a random element, (3) requesting allocation for participants by four different study nurses, and (4) not disclosing full details of minimization to study nurses in accordance with the SPIRIT guideline [57]. Further details, including the rationale for the selection of minimization factors, are provided in Section 1 of the Supplementary Material.

Intervention and control condition

The exercise and control interventions started at approximately 04:45 pm in the afternoon. Patients allocated to the intervention group performed a single bout of supervised aerobic exercise on a bicycle ergometer (ergoselect 200, Ergoline, Bitz, Germany). The intervention began with a 5-minute warm-up period in which the intensity was gradually increased. Thereafter, patients exercised at an intensity of 80% of the individual anaerobic threshold (i.e. as defined by graded exercise testing) for 30 min (i.e. as recommended by guidelines [24]). We recorded average Watt and heart rate (Polar H7 chest strap, Polar OY, Finland) as well as perceived exertion in the 5th, 15th, and 30th min in the exercise group. Patients allocated to the control group were asked to sit and read magazines when the intervention group was exercising. All patients completed a mood questionnaire (*Befindlichkeitsskala*) [58] directly before and after the intervention. This questionnaire consists of 40 adjectives (e.g. cheerful, sad) with a five-point Likert scale (*1 = not at all* to *5 = very much*) to indicate the experience of these adjectives in the present moment. Items load onto eight subscales (with five items each): activity, elation, contemplation, calmness, fatigue, depression, anger, and excitement. We also administered six Likert scaled (*1 = not at all* to *5 = very much*) questions on adverse outcomes (pain, dizziness, cardiovascular symptoms, respiratory symptoms, nausea, and "other") immediately after the intervention.

We took multiple measures to offset the risk of performance bias that is inherent to exercise trials. Patients were instructed not to perform any other physical exercise except their daily activities. All patients wore an accelerometer (vivofit 2, Garmin, Schaffhausen, Switzerland) on their nondominant wrist on the days before and after the sleep assessments. The validity of this is accelerometer has been demonstrated [59]. The accelerometer data allowed us to gauge potential contamination through other physical activity. Moreover, the rules and schedules of the in-patient rehabilitation clinic (e.g. timing of meals, consumption of multimedia, and alcohol) limit the variability of many behavioral aspects and ancillary treatments which could influence sleep.

Follow-up assessments

We repeated objective and subjective sleep assessments at follow-up identically to baseline (see Figure 1). Also, we administered the adverse outcomes question upon awakening. Lastly, the Stanford Sleepiness Scale [60] was administered four times (08:00 am, 12:00 pm, 04:00 pm, 08:00 pm) on the day after the intervention to assess excessive daytime sleepiness.

Outcomes

Polysomnographic sleep efficiency was the primary outcome. We chose a polysomnographic variable because the inability to blind patients against allocation in exercise trials increases the risk of a detection bias for patient-reported outcomes. Patients with depression have difficulties initiating and maintaining sleep, and they also show early morning awakening [61]. Sleep efficiency is an appropriate polysomnographic measure to capture these sleep problems. We defined multiple secondary outcomes which should help to inform clinical decision-making. Secondary polysomnographic outcomes were: total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO), number of awakenings (NA), stage one sleep (N1; in percent of TST), stage two sleep (N2; in percent of TST), stage three sleep (N3; in percent of TST), non-REM sleep (in percent of TST), REM sleep (in percent of TST), REM-sleep latency (minutes), and stage shift index (stage changes per hour). Secondary subjective outcomes were subjective sleep quality, daytime sleepiness, mood states, and adverse events. The secondary outcomes of presleep arousal and nocturnal autonomic cardiovascular modulation prespecified in the protocol will be published in a different paper.

Statistical methods

We analyzed the primary outcome using an ANCOVA model. Thereby, we used baseline sleep efficiency and minimization factors [62] as covariates, allocation as the independent variable, and follow-up sleep efficiency as the dependent variable. First, we checked the statistical prerequisites. If residuals were heteroscedastic, we used heteroscedasticity-consistent estimation of the covariance matrix (HC3) [63]. We used intent-to-treat analysis to reduce attrition bias. We replaced missing values using multiple imputations [64]. Sensitivity analyses for the primary outcome were performed to gauge the influence of several factors: influential data points, per-protocol analysis (to reflect optimal adherence to treatment), missing data (analysis of complete data only), and chronotypes. All analyses were performed using the software R, version 3.6.3 [65].

Sample size calculation was performed according to the procedure defined by Borm et al. [66]. The expected treatment effect is based on the work of Passos et al. [67], which found a standardized mean difference in polysomnographic sleep efficiency of 0.53 (detailed rationale for the choice of this effect size is provided in the protocol [25]). With a power of 0.8 and a two-sided alpha of 0.05, 57 subjects would be required for each group using a *t*-test. According to the method of Borm et al., this sample size can be multiplied by a "design factor" of $(1 - \rho^2)$, where ρ is the correlation coefficient between baseline and follow-up outcome [66]. We used a conservative estimate and let $\rho = 0.5$, resulting in a "design factor" of 0.75 $(1 - 0.5^2 = 0.75)$. Hence the sample size needed per group is 43 $(57 \times 0.75 = 42.75)$. We anticipated a dropout rate of approximately 7% (half the average dropout rate of trials investigating the chronic effects of exercise in patients with depression [68]). Therefore, we calculated the total sample size to be 92 $(2 \times 43 \times 1.07 = 92)$.

The choice of statistical analysis for secondary outcomes was based on the number of assessments for each outcome. We calculated the effect of allocation using ANCOVA models (as outlined for the primary outcome) for all outcomes assessed at baseline and follow-up. We analyzed acute daytime sleepiness (four measurements) using a two-way repeated-measures ANOVA with Benjamini-Hochberg [69] corrected post hoc paired sample *t*-tests. We assessed adverse outcomes using Mann-Whitney-U tests. The threshold for statistical significance was set at $p \leq 0.05$. We did not adjust secondary analyses for multiple testing, and thus these should be considered exploratory.

Results

Four hundred and forty-eight patients were screened for inclusion between September 2018 and January 2020 (see Figure 2). The most frequent reason for exclusion was the use of hypnotics (48%), followed by exercise contraindications (13%), and not being diagnosed with unipolar depression (8%). Ninety-two patients met eligibility criteria and were allocated to moderate aerobic exercise ($N = 46$) or the control condition ($N = 46$). Baseline characteristics of the study sample are summarized in Table 2. Demographic and clinical characteristics were well balanced at baseline. Four patients did not complete the study (two in each group). Dropouts did not seem to differ from completers at baseline. In addition to the dropouts, two polysomnographic measurements at follow-up failed (one in each group), and five patients did not complete the subjective sleep questionnaires. Inter-rater reliability was good (Cohen's Kappa: wake: 0.82; N1: 0.49; N2: 0.68; N3: 0.73; REM: 0.79). The intervention was implemented as planned: the mean rate of perceived exertion was 13.6 ($SD = 1.6$), and the mean percent of age-predicted maximal heart rate over the course of the intervention was 70.6% ($SD = 6.8\%$), see Supplementary Figures S1 and S2. There was no evidence to suggest that average daily steps differed between the groups, $F(1.82, 144.14) = 0.08$, $p = 0.9$.

Intent-to-treat analysis ANCOVA of follow-up sleep efficiency, adjusted for pre-intervention levels and minimization factors did not detect a significant effect of the allocation, see

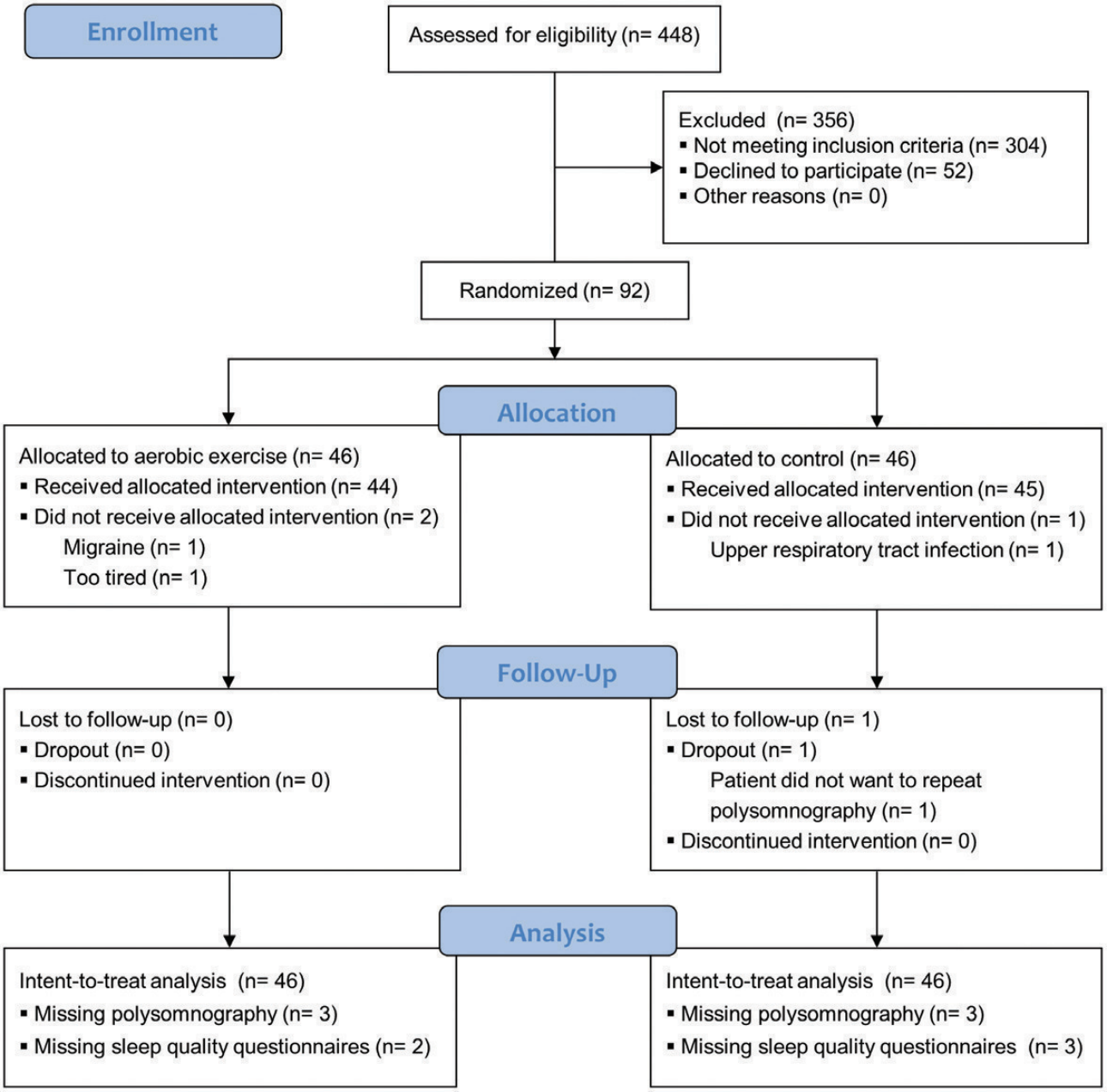

Figure 2. CONSORT participant flow.

Table 3 and Figure 3. The coefficient for allocation is the difference between the mean change scores of each group.

This finding was robust in all sensitivity analyses. Prespecified sensitivity analyses included per protocol (i.e. only including patients who reported an RPE (rate of perceived exertion) value of ≥13 at the end of the exercise intervention) and complete case (i.e. not using imputed data) analyses. Furthermore, we identified one influential data point (based on Cook's distance and DFBETA), clearly visible in Figure 3. Excluding this observation did not alter the primary ANCOVA results or any of the other aforementioned sensitivity analyses. There were no significant interaction effects of chronotype (β = 0.20, 95% CI = −0.08 to 0.47, p = 0.19), expectancy (β = −2.33, 95% CI = −8.43 to 3.79, p = 0.45), and credibility (β = −4.17, 95% CI = −12.54 to 4.19, p = 0.32) with allocation. There was no evidence that the rate of perceived exertion (r_s = 0.05, p = 0.76) nor the average percent of age-predicted maximal heart rate (r_s = −0.16, p = 0.30) was associated with sleep efficiency in the intervention group at follow-up. Steps on day four (measured by accelerometer) did not predict sleep efficiency at follow-up in the ANCOVA model (β = −0.10, 95% CI: −0.46 to 0.25, p = 0.56; for ease of interpretation, step count was divided by 1,000).

There was no evidence for an effect of allocation on any other objectively or subjectively measured sleep outcomes. The effect of allocation on polysomnographic and subjective sleep outcomes are summarized in Tables 4 and 5, respectively. The internal consistency of the sleep questionnaire subscales was adequate (Cronbach's alpha: sleep quality = 0.87; recuperation after sleep = 0.93; mental balance before sleep = 0.90; exhaustion before sleep = 0.68; nocturnal psychosomatic symptoms = 0.65).

Table 2. Patient characteristics at baseline

		Control (*N* = 46)	Exercise (*N* = 46)
Age		47.50 [43, 51]	46.00 [37, 53]
Sex	Female	33 (71.7)	32 (69.6)
	Male	13 (28.3)	14 (30.4)
BMI		24.4 [22.2, 27.7]	25.0 [21.8, 29.2]
PHQ15		12.5 [8.0, 14.0]	12.5 [8.3, 15.8]
CIRS		3.0 [1.3, 5.0]	3.5 [2.0, 4.8]
PHQ9		15.0 [12.0, 17.0]	14.0 [12.0, 17.0]
HADS anxiety		11.5 [9.0, 14.0]	11.0 [9.3, 14.0]
PSS10		26.0 [21.3, 28.0]	27.0 [22.0, 29.0]
MEQ		56.5 [47.0, 61.8]	51.0 [45.3, 59.0]
DBAS		4.8 [3.8, 5.4]	4.6 [3.6, 5.7]
FIRST		27.5 [21.3, 29.8]	27.0 [24.0, 29.8]
ESS		10.0 [7.0, 12.0]	9.0 [6.0, 11.0]
PSQI		9.5 [6.3, 12.0]	10.0 [7.00, 13.75]
Oxygen desaturation index*		1.8 [0.7, 3.9]	2.1 [0.7, 3.9]
Sleep efficiency*		88.8 [82.5, 94.0]	91.3 [84.4, 93.5]
Total sleep time*		416.7 [382.3, 463.1]	439.0 [393.3, 479.5]
Sleep onset latency*		14.5 [6.8, 27.2]	14.0 [5.5, 23.3]
Wake after sleep onset*		37.8 [19.1, 62.6]	30.8 [18.0, 43.3]
Number of awakenings*		15.8 [11.4, 20.8]	17.0 [13.5, 23.5]

*Measured polysomnographically.
Continuous variables are presented as medians with interquartile ranges (median [Q_1, Q_3]) and sex is presented as absolute numbers and percentages (*N* (%)). BMI, body mass index; PHQ15, Patient Health Questionnaire 15; CIRS, Cumulative Illness Rating Scale; PHQ9, Patient Health Questionnaire 9; HADS anxiety: Hospital Anxiety and Depression, anxiety subscale; PSS10, Perceived Stress Scale, 10 item version; MEQ, Morningness-Eveningness Questionnaire; DBAS, Dysfunctional Beliefs and Attitudes about Sleep Scale; FIRST, Ford Insomnia Response to Stress Test; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.

Table 3. ANCOVA table for intent-to-treat analysis of sleep efficiency at follow-up

Term	Estimate (β)	Standard error (β)	95% confidence interval		*P*
Intercept	59.50	18.79	22.09	96.91	0.002
Baseline sleep efficiency	0.42	0.19	0.03	0.80	0.03
Age	−0.05	0.10	−0.25	0.15	0.61
Sex (male*)	−0.98	1.87	−4.70	2.74	0.60
PHQ9 score	−0.20	0.22	−0.64	0.23	0.36
PSQI score	−0.08	0.22	−0.52	0.37	0.73
Allocation (exercise†)	−0.93	1.70	−4.32	2.47	0.59

*Sex was coded as follows: 1 = male, 2 = female.
†Exercise was coded as follows: 1 = control, 2 = exercise.
Age, sex, PHQ9 score, and PSQI score were entered as covariates because they were used as minimization factors.
PHQ9, Patient Health Questionnaire 9; PSQI, Pittsburgh Sleep Quality Index.

There was no evidence for an effect of allocation on daytime sleepiness over time, $F(3, 222) = 1.15$, $p = 0.33$. Post-hoc tests assessing the effects of allocation were not significant (see Supplementary Figure S3).

Next, we investigated the effects of exercise on mood. All subscales of the mood questionnaire showed good internal consistency (Cronbach's alpha > 0.8) except the subscale contemplativeness (Cronbach's alpha: 0.47 and 0.64 for pre- and post-intervention, respectively). Hence, we did not further analyze the items of the subscale contemplativeness. ANCOVAs of post-intervention mood, adjusted for pre-intervention levels and minimization factors showed that exercise consistently improved mood. Patients in the intervention group reported higher levels of activation (β = 0.85, 95% CI: 0.52 to 1.19, $p < 0.001$), elation (β = 0.59, 95% CI: 0.36 to 0.82, $p < 0.001$), and calmness (β = 0.49, 95% CI: 0.24 to 0.75, $p < 0.001$), as well as less agitation (β = −0.48, 95% CI: −0.85 to −0.12, $p = 0.005$), depressiveness (β = −0.40, 95% CI: −0.66 to −0.14, $p = 0.003$), fatigue (β = −0.91, 95% CI: −1.13 to −0.45, $p < 0.001$), and anger (β = −0.26, 95% CI: −0.51 to −0.01, $p = 0.04$).

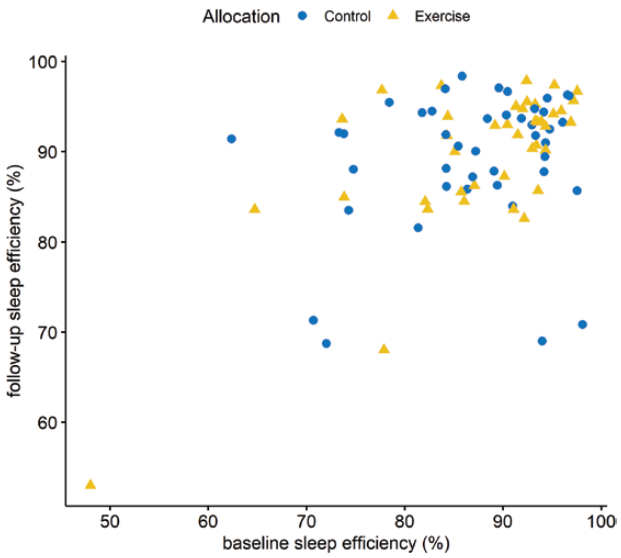

Figure 3. Baseline and follow-up sleep efficiency by allocation.

We did not find evidence for an effect of allocation on adverse outcomes. There were no serious adverse events in either group. We aggregated the questions on adverse outcomes since they showed satisfactory internal consistency at both time points (Cronbach's alpha: 0.76 and 0.73). The number of reported symptoms immediately after the intervention did not differ between the groups. However, immediately after the intervention there was a trend toward lower symptom severity in the intervention group (median = 0.29) compared to the control group (median = 0.46; $r = 0.19$, $p = 0.08$). Upon awakening on the day after the intervention, there was no evidence to suggest that the group differed in terms of adverse outcome frequency or intensity.

Discussion

The main goal of our trial was to investigate the effects of 30 min of moderate aerobic exercise in patients with depression on the subsequent night's sleep efficiency measured by polysomnography. Secondary goals were to assess the effects on other objectively and subjectively measured sleep outcomes, mood, and adverse effects.

We did not find evidence to suggest that a single bout of moderate aerobic exercise improves polysomnographically or subjectively measured sleep outcomes. The absence of evidence for an effect of allocation was very consistent. None of the sensitivity analyses of the primary outcome nor of the secondary

Table 4. Coefficients of exercise allocation in ANCOVA models predicting polysomnographic outcomes

Outcome	Estimate for exercise allocation* (β)	Standard error (β)	95% Confidence interval		P
Total sleep time	−0.50	11.86	−24.09	23.10	0.97
Sleep onset latency	−1.15	3.39	−7.89	5.60	0.74
Wake after sleep onset	1.86		−11.32	15.04	0.78
Number of awakenings	−1.70	1.28	−4.24	0.84	0.19
Stage shift index	0.04	0.61	−1.18	1.26	0.95
N1 (% TST)	−1.4	0.91	−3.21	0.42	0.13
N2 (% TST)	0.94	1.64	−2.34	4.21	0.57
N3 (% TST)	0.55	1.32	−2.07	3.16	0.68
REM (% TST)	−0.02	1.10	−2.21	2.18	0.99
REM latency	4.20	10.76	−17.23	25.64	0.70

*Allocation was coded as follows: 1 = control, 2 = exercise.
All models used baseline values of the outcome as well as minimization factors (sex, age, PHQ9 score, and PSQI score) as covariates and allocation as the independent variable. The coefficient for allocation is the difference of the mean change score in the exercise group compared to the control group.
N1, stage one sleep, N2, stage two sleep, N3, stage three sleep, REM, rapid eye movement sleep, TST, total sleep time.

Table 5. Coefficients of exercise allocation in ANCOVA models predicting subjective sleep outcomes

Outcome	Estimate for exercise allocation* (β)	Standard error (β)	95% Confidence interval		P
Exhaustion before sleep	0.15	0.15	−0.15	0.44	0.32
Mental balance before sleep	0.00	0.18	−0.35	0.36	0.99
Nocturnal psychosomatic symptoms	0.03	0.09	−0.15	0.21	0.73
Recuperation after sleep	0.31	0.17	−0.01	0.64	0.06
Sleep quality	0.20	0.19	−0.18	0.58	0.31

*Allocation was coded as follows: 1 = control, 2 = exercise.
All models used baseline values of the outcome as well as minimization factors (sex, age, PHQ9 score, and PSQI score) as covariates and allocation as the independent variable. The coefficient for allocation is the difference of the mean change score in the exercise group compared to the control group.

polysomnographic or of the subjective sleep outcomes found a significant effect.

This is the first trial to study the *acute* effects of a single bout of aerobic exercise on sleep in patients with depression to the best of our knowledge. Trials investigating the effects of a single bout of exercise on objectively and subjectively measured sleep in patients with insomnia, however, have found equivocal evidence. While two trials [70, 71] found no effect of exercise on sleep, three trials found some positive effects on objectively measured sleep [67, 72, 73]. The first trial found beneficial effects on sleep onset latency, total sleep time, and sleep efficiency [67]. The second study observed positive effects on actigraphically measured sleep latency and sleep efficiency [73]. The third investigation showed a reduction in stage shifts during the entire night as well as a reduction in stage shifts, arousal index, and wake stages during the second half of the night following exercise performed in the morning [72]. The different findings cannot be readily explained by moderating factors like exercise intensity, duration, or timing. The only trial in which exercise was implemented in the morning revealed a significant effect [72]. Exercising in the afternoon or evening produced mixed results, with some trials finding beneficial [67, 73] and others finding no effect [70–72].

While two trials [70, 71] found no effect of exercise on sleep, three trials found some positive effects on objectively measured sleep [67, 72, 73]. Passos et al. found beneficial effects on sleep onset latency, total sleep time, and sleep efficiency [67]. Li-Jung et al. observed positive effects on actigraphically measured sleep latency and sleep efficiency [73]. Morita et al. showed a reduction in stage shifts during the entire night as well as a reduction in stage shifts, arousal index, and wake stages during the second half of the night following exercise performed in the morning [72]. The different findings cannot be readily explained by moderating factors such as intensity, duration, or timing of the exercise. The only trial in which exercise was implemented during the morning hours revealed a significant effect [72]. Exercising in the afternoon or evening produced mixed results, with some trials finding beneficial [67, 73] and others finding no effect [70–72].

There are several explanations as to why we did not find evidence for the effect of exercise on sleep in this trial. First, issues of internal consistency might have played a role. However, our study design makes this explanation unlikely for the following reasons. We can rule out contamination from other physical activity since step count did not differ between groups and step count was not a significant covariate. There were no differences between the groups at baseline. Moreover, the in-patient rehabilitation setting limits the variability of behavioral aspects which can influence sleep. Second, the trial might have been underpowered due to inappropriate assumptions. Our sample size calculation is based on an effect size for aerobic exercise found in patients with insomnia (a detailed rationale of the sample size calculation can be found in the protocol [25]). However, in our study, polysomnographic outcomes were within the range of healthy individuals [74, 75]. This finding is most likely due to the exclusion of patients who regularly used hypnotics, thus excluding patients with severe insomnia. Reported effect sizes of aerobic exercise on sleep in healthy individuals are smaller [76] than the effect size we used for our sample size calculation. Hence, it is possible that our trial was underpowered

to detect a significant difference. Third, a single bout of aerobic exercise might not affect sleep in patients with depression. We cannot provide evidence for the absence of an effect in superiority trials. Thus a non-inferiority trial is needed to provide evidence for the second or third explanation.

The immediate effects of the exercise intervention on mood states were consistently positive. Negative mood states decreased, notably including depressiveness, and positive mood states increased. Findings on the acute effects of moderate aerobic exercise on mood states in patients with depression have been equivocal to a certain degree. While all trials have found positive effects for at least some mood subscales, some have found positive effects on all mood subscales. Our findings are consistent with Niedermeier et al. [77], which also found increased positive and decreased negative mood states with large effect sizes. Stark et al. [78], Frühauf et al. [79], Bartholomew et al. [80], and Legrand et al. [81] also found positive effects on some but not all mood states. Of note, the trial of Stark et al. [78] implemented the same questionnaire as we did, but the intervention lasted 60 min. They found significant and substantial beneficial effects for all subscales except anger. The inconsistencies between the studies mentioned above are likely due to small sample sizes and different outcome questionnaires, which measure slightly different facets of mood.

Adverse outcome severity immediately after the intervention tended to be slightly lower in the intervention group. Although this was a nonsignificant trend and the effect size was small, it is important to note that there is no evidence that exercise increased pain, dizziness, nausea, or cardiovascular and respiratory symptoms. Adverse events are a central aspect of clinical decision-making [46]. However, adverse effects (i.e. an undesirable symptom or outcome temporally associated with an intervention) are underreported in exercise [82] and sleep [46] trials. There are no trials on the acute effects of exercise, which included patients with depression and reported adverse outcomes to the authors' knowledge. The meta-analysis of Krogh et al. [83] analyzed the chronic effects of exercise in patients with depression. Only approximately 10% and 30% of the included trials reported data on serious and nonserious adverse events, respectively. Based on this limited data, Krogh et al. found that allocation to exercise interventions was associated with a lower risk of nonserious but an increased risk of serious adverse events [83]. The meta-analysis of Niemeijer et al. found no evidence of an increased risk for nonserious adverse events in the psychiatric subgroup [82]. Thus, our study helps to close the gap in the literature concerning the adverse effects of exercise.

This study has several strengths. We took several measures to minimize the risk of bias. These include using minimization (a restricted randomization technique) as well as solid allocation concealment (selection bias), blinding scorers of polysomnographic data (detection bias), quantifying contamination through other physical activity (performance bias), and intent-to-treat analysis (attrition bias). We also carefully selected secondary outcomes which help to inform clinicians, patients, and policymakers. Both scorers have demonstrated good agreement with gold standard ratings of the AASM inter-scorer program [52]. The inter-rater agreement in this trial was within the range reported by other sleep centers [84, 85]. Furthermore, the absence of evidence for an effect of allocation on sleep outcomes and the strong positive effect on the different mood subscales are very consistent.

Limitations include the restricted external validity and the limited polysomnographic montage. The inclusion of patients with psychiatric and somatic comorbidities enhanced the external validity of this study. However, we excluded many of the screened patients because of hypnotics. Although this increased internal validity, it limited external validity. The limits to external validity should be considered when using these findings to inform clinical practice. It is unclear whether the present findings are transferable to patients who regularly use hypnotics. We also made a conscious trade-off between feasibility (reduced polysomnographic montage) and the resulting loss of information. The reduced montage did not allow us to analyze EEG microarchitecture. The strengths and limitations highlighted above point to interesting avenues for future research.

The findings of our study have several scientific implications worth mentioning. Future trials can improve our understanding of exercises' effects on sleep in patients with depression in many ways. Effectiveness trials could compare the acute effects of different interventions commonly used in in-patient or outpatient treatment settings (e.g. relaxation or mindfulness interventions, light therapy). Importantly, these trials should include patients who use hypnotics. A particularly promising line of investigation is whether exercise is an effective add-on treatment to psychotherapy, pharmacotherapy, or both. The effect of exercise timing is also interesting. The timing of exercise throughout the day seems to alter exercises' effects on sleep in healthy individuals [76]. This finding might be partially explained by the different effects morning and evening exercise have on melatonin secretion at 10:00 pm [86] and on circadian phase shifts (the latter also depends on the chronotypes) [87]. Any trial on the effects of exercise in patients with depression should systematically collect and report data on adverse effects. Non-inferiority trials could show that exercise does not increases the risk of adverse outcomes. Despite the remaining research questions, this trial can improve clinical decision-making.

These findings can inform clinical practice in multiple ways. A single bout of moderate aerobic exercise will improve mood states and is likely not to have harmful effects on sleep or other symptoms. In addition, patients can expect positive effects on sleep (and many other outcomes, including depressiveness) if they continue to exercise over multiple weeks or months. Our findings also add to the growing body of evidence that exercise performed after 02:00 pm does not reduce sleep quality. This body of evidence is in contrast to current sleep hygiene recommendations [21]. Meta-analyses in healthy populations of all ages have also consistently confirmed that exercise after 02:00 pm either has no effect or even improves sleep [23, 76, 88]. Trials focusing on patients with insomnia have found similar results, although there are far fewer trials available [67, 70–73]. This is relevant to therapeutic settings where exercise interventions are commonly also implemented after 02:00 pm.

Conclusions

In conclusion, this trial suggests that a single bout of moderate aerobic exercise strongly improves mood but found no evidence for an effect on the subsequent night's sleep or adverse outcomes. This is the first trial to study the effects of a single bout of exercise on sleep in patients with depression to the best of our knowledge. Additional non-inferiority trials are needed to confirm that moderate aerobic exercise does not negatively affect sleep nor increase the risk of adverse outcomes.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Ethics Approval

The study protocol was approved by the Ethics Committee East Switzerland, St. Gallen, Switzerland (EKOS 18/089). All participants provided written informed consent prior to enrollment and could revoke their consent at any time.

Authors' Contributions

GB, TZS, DS, HP, MG, RvK, and AST contributed to the design. GB conceived the trial design, wrote the manuscript, and managed the overall project. TZS and GB scored the polysomnography. DI advised the statistical analysis. All authors revised the manuscript and approved the final version.

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Supplement

Section 1: Minimization scheme of EASED trial

A nondeterministic unweighted minimization algorithm with a random element of 0.8 will be used to increase the probability of balanced groups. The allocation ratio is 1:1. Allocation to intervention or control group will be done using the open source software for online minimization (Oxford Minimization and Randomization, OxMaR)[1]. The following factors and corresponding classes will be used for minimization:

- sex (male, female)
- age in years (18-26, 27-36, 37-46, 47-56, 57-65)
- depression severity measured by PHQ-9 score (0-4, 5-9, 10-14, 15-19, 20-27)
- sleep quality measured by PSQI score (0-4, 5-10, 11-16, 17-21)

These variables were chosen because previous studies have shown that the effect of exercise on sleep may vary between gender[2], objectively measured sleep characteristics change linearly throughout adulthood[3], and sleep quality as well as depression severity might alter effectiveness of the intervention. Age classes are created by dividing the age range as equally as possible in five classes. Depression severity classes are based on validated cut-offs for no, mild, moderate, moderately severe, and severe depression[4]. In the sleep quality factor, the validated cut-off (≥5) is used to delineate the first class[5]. Since most patients are above this cut-off, the remaining range of scores is further divided into even classes.

A simulation using the software SiMin[6] with 5000 iterations was performed to estimate the discrepancies between the groups using the above mentioned specifications. The mean discrepancies between the exercise and control group are estimated to be 1.83 for gender, 2.59 for PSQI score, and 3.42 for age as well as PHQ-9 score. With a probability of 0.95 the discrepancy between groups will not exceed 4 patients for sex and 5 patients for age, PHQ-9 score, and PSQI-score. The simulation showed that weighting factors caused an increase in the discrepancy of sex while not affecting the other variables. Therefore, factors will not be weighted in the minimization.

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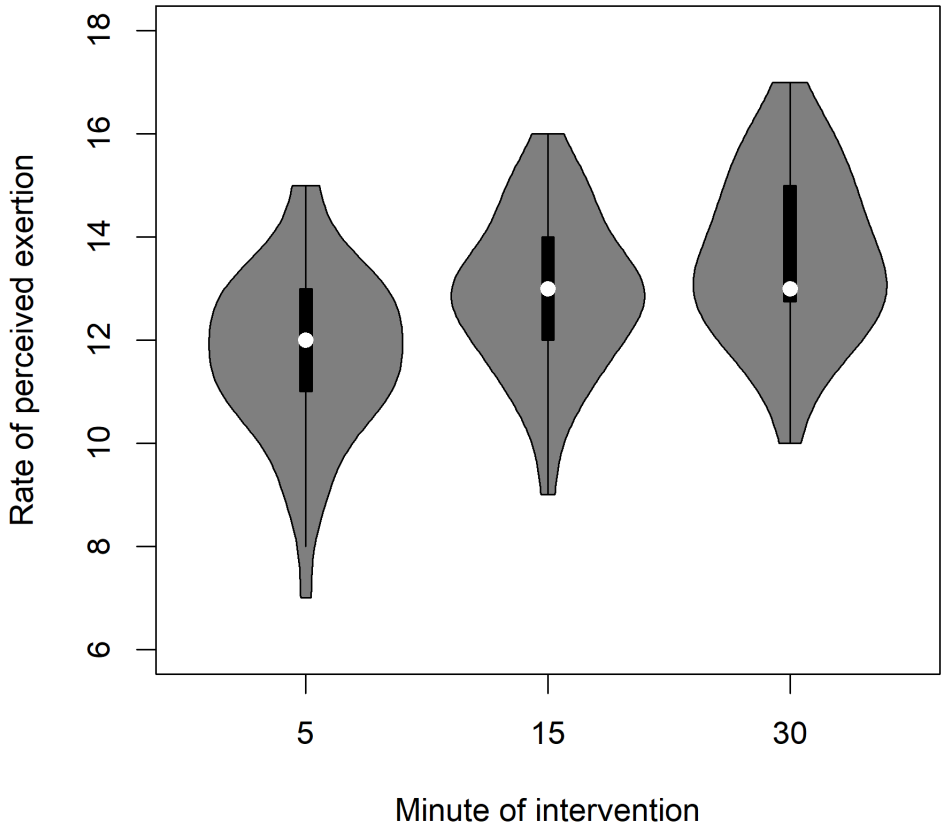
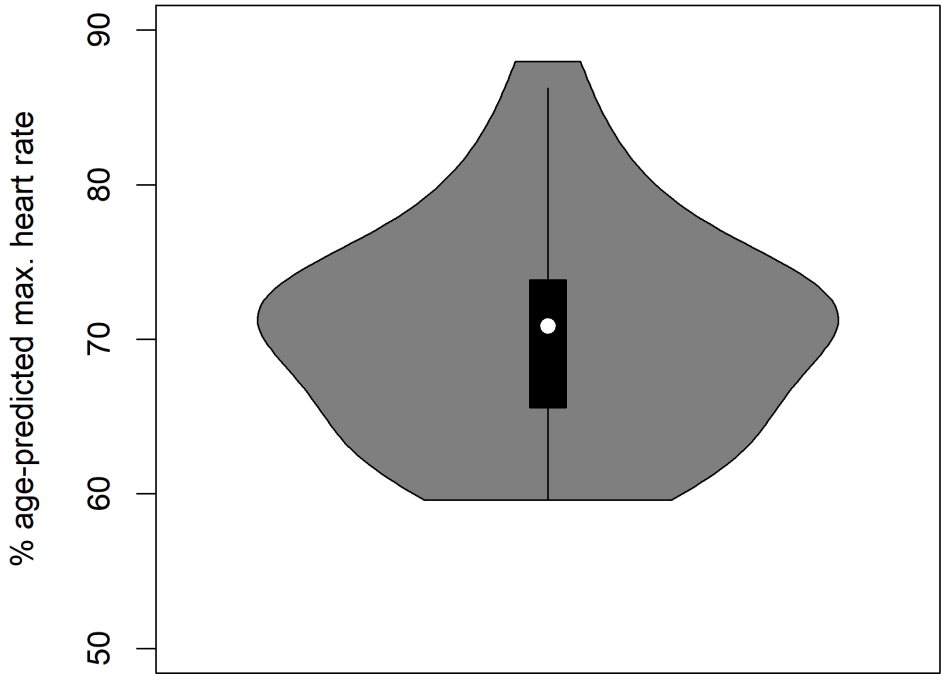
Figure S1: Rate of perceived exertion during the intervention



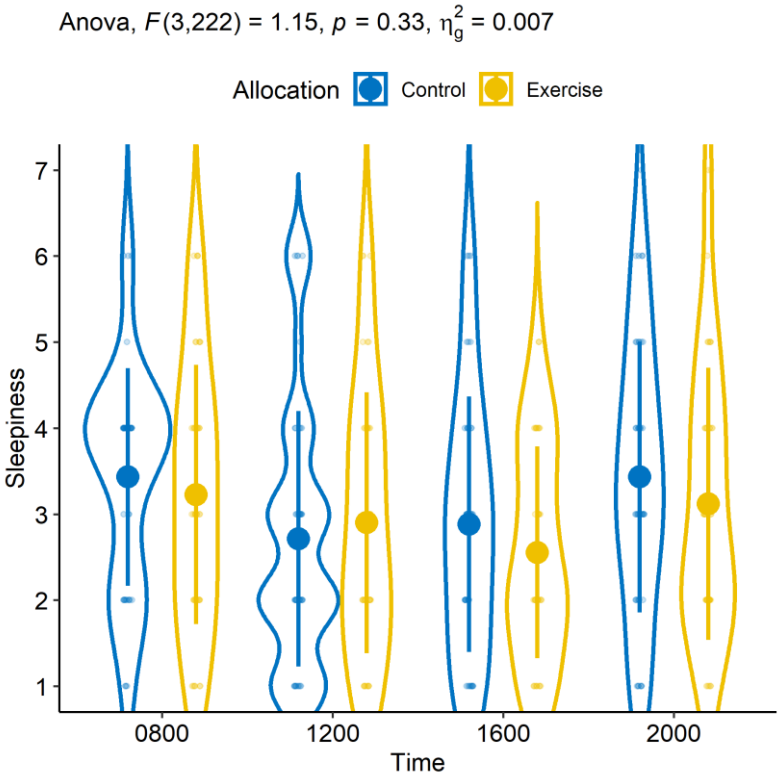
Note: rate of perceived exertion is rated on a scale from 6 to 20.

Figure S2: Average heart rate during the intervention



Note: age-predicted heart rate is calculated according to the formula of Tanaka et al., 2001, i.e., 208 − 0.7 × age.

Figure S3: Daytime sleepiness



Chapter 7

Publication 5: The acute effects of aerobic exercise on nocturnal and pre-sleep arousal in patients with unipolar depression: a randomized controlled trial

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Article

The Acute Effects of Aerobic Exercise on Nocturnal and Pre-Sleep Arousal in Patients with Unipolar Depression: Preplanned Secondary Analysis of a Randomized Controlled Trial

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Abstract: Unipolar depression is associated with insomnia and autonomic arousal. The aim of this study was to quantify the effect of a single bout of aerobic exercise on nocturnal heart rate variability and pre-sleep arousal in patients with depression. This study was designed as a two-arm, parallel-group, randomized, outcome assessor-blinded, controlled, superiority trial. Patients with a primary diagnosis of unipolar depression aged 18–65 years were included. The intervention consisted of a single 30 min moderate-intensity aerobic exercise bout. The control group sat and read for 30 min. The primary outcome of interest was RMSSD during the sleep period assessed with polysomnography. Secondary outcomes were additional heart rate variability outcomes during the sleep and pre-sleep period as well as subjective pre-sleep arousal. A total of 92 patients were randomized to either the exercise ($N = 46$) or the control ($N = 46$) group. Intent-to-treat analysis ANCOVA of follow-up sleep period RMSSD, adjusted for baseline levels and minimization factors, did not detect a significant effect of the allocation ($\beta = 0.12$, $p = 0.94$). There was no evidence for significant differences between both groups in any other heart rate variability measure nor in measures of cognitive or somatic pre-sleep arousal. As this is the first trial of its kind in this population, the findings need to be confirmed in further studies. Patients with depression should be encouraged to exercise regularly in order to profit from the known benefits on sleep and depressive symptoms, which are supported by extensive literature.

Keywords: aerobic exercise; depression; heart rate variability; polysomnography; sleep; pre-sleep; arousal

1. Introduction

Insomnia and unipolar depression are bidirectional risk factors for one another [1–4]. Up to 90% of patients with unipolar depression report symptoms of insomnia [5–8]. Insomnia has detrimental effects on disease trajectory [9–13]. Insomnia is also the most frequent residual symptom after remission [5,14], which in turn increases the risk of relapse [15,16].

Arousal is a central characteristic and possibly a common pathophysiological mechanism of insomnia and depression. The hyperarousal model postulates that arousal pro-

cesses in multiple physiological systems cause insomnia [17]. The cognitive model of insomnia hypothesizes that excessive negative thoughts trigger autonomic arousal, which maintains insomnia [18]. The arousal regulation model of affective disorders posits that sensation avoidance and withdrawal in unipolar depression are an autoregulatory reaction to neurophysiologic hyperarousal [19]. Indeed, insomnia [17,20] and depression [21–26] have been empirically shown to be associated with somatic, cortical, and cognitive hyperarousal.

Heart rate variability (HRV) is a universally acknowledged marker for arousal in the context of unipolar depression for multiple reasons. It is well established that a clinical diagnosis of depression and depression severity are associated with lower HRV during the day [27–31] and night [32–36]. Lower HRV is also observed during and immediately after exercise in patients with depression [37]. Moreover, there is evidence to suggest that reduced HRV is an antecedent to depression [38,39]. Reduced HRV is a pathophysiological mechanism [40–43] explaining the increased risk of cardiovascular disease (CVD) in patients with depression [44–46].

There is no evidence that psychotherapy and antidepressants, i.e., guideline treatments for depression, increase HRV in this population. On the contrary, tricyclic antidepressants have been unequivocally shown to lower HRV [28,47–51]. Other antidepressants (e.g., selective noradrenaline or serotonin reuptake inhibitors) have produced mixed results, suggesting no effect or a reduction in HRV [28,47–51]. Combined psychotherapy and psychopharmacotherapy do not seem to increase HRV, despite strongly ameliorating depressive symptoms [52]. However, there is evidence that biofeedback [53–55] and breathing exercises [56] (as standalone or add-on therapies) increase HRV in patients with depression. Moreover, a considerable portion of patients with depression fail to remit when treated with guideline therapies [57–59]. Failure to remit increases the risk for CVD in patients who were initially free of CVD [60–64]. There is a need for further adjuvant therapies that lower arousal during the night in patients with depression, considering the evidence presented above.

Exercise is a promising behavioral adjuvant treatment to lower arousal in depression. Chronic mind–body [65,66] exercise and aerobic exercise [67,68] have been shown to improve HRV in patients with depression. Regular exercise increases HRV in healthy individuals [69,70] and patients with CVD [71,72], as reviews and meta-analyses have shown. We have recently demonstrated that chronic exercise has positive effects on sleep in patients with depression [73]. However, acute bouts of physical activity might have adverse effects. This is reflected in current sleep hygiene recommendations, which state that exercise should not be performed after 2 pm, as this might increase arousal [74]. Findings on the acute effect of moderate-intensity aerobic exercise on the subsequent night's HRV have been equivocal. While most trials did not detect a difference in nocturnal HRV [75–81], one study found that moderate aerobic exercise decreased HRV [82]. To our knowledge, there are no trials investigating the acute effects of a single bout of aerobic exercise on HRV in depression. Moreover, we are not aware of any trial investigating the acute or chronic effects of exercise on pre-sleep arousal. Hence, there is a gap in the literature concerning arousal-reducing adjuvant therapies for patients with depression.

Considering the relevance of sleep for patients with depression outlined above, we chose to study the effects of exercise on nocturnal arousal. Therefore, the primary aim of this trial was to quantify the effect of a single bout of aerobic exercise on nocturnal arousal measured by HRV during sleep in patients with depression. Secondary aims were to investigate intervention effects on pre-sleep HRV and pre-sleep arousal. We hypothesized that the intervention would significantly decrease (1) nocturnal, (2) pre-sleep HRV, and (3) subjective pre-sleep arousal.

2. Methods

This study was a two-arm, parallel-group, randomized, controlled, outcome assessor-blinded, superiority trial. We recruited patients within the psychosomatic in-patient rehabilitation unit of the clinic OBERWAID in St. Gallen, Switzerland. The study was

conducted in accordance with the Declaration of Helsinki [83], and the Ethics Committee East Switzerland, St. Gallen, Switzerland approved the study protocol (EKOS 18/089). We prospectively registered the trial in the clinicaltrial.gov registry on 17 September 2018 (NCT03673397). We published a detailed study protocol with the study's rationale [84]. There were no amendments. Analysis of nocturnal HRV deviates from the published protocol. We chose the method presented here because it allows for a more precise analysis than hourly segments after falling asleep. We adhere to the CONsolidated Standards of Reporting Trials (CONSORT) [85] and the Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH) [86] guidelines in this publication. The data underlying this article are available in the Harvard Dataverse at https://doi.org/10.7910/DVN/WASN36 and will be shared at reasonable request to the corresponding author. The focus of this paper is on the secondary outcomes of HRV, while the primary outcome is presented elsewhere [87].

2.1. Participants

We screened patients who were admitted to the in-patient psychosomatic rehabilitation unit of the clinic OBERWAID. We conducted the trial in the first five days of the psychosomatic in-patient rehabilitation. The first author or another representative of the clinic OBERWAID obtained written informed consent from all participants involved in the study. Inclusion criteria were: (1) 18–65 years old and (2) a diagnosis of depression (confirmed by experienced psychiatrists according to ICD-10). We applied the following exclusion criteria: (1) regular use of hypnotic agents (patients were included if no hypnotic agents were taken two weeks before study participation), (2) factors precluding exercise testing or training according to the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription [88], (3) use of beta-blockers (except carvedilol and nebivolol), (4) use of opioids, (5) history of epilepsy, (6) restless legs syndrome (defined by the validated cut-off in the restless legs syndrome screening questionnaire [89]), (7) oxygen desaturation index ≥ 15 (indicative of at least moderate sleep apnea) in the baseline polysomnography, and (8) BMI > 40. We provide a rationale for each criterion in our study protocol [84].

2.2. Patient Characteristics

We implemented multiple assessments to characterize patients at baseline. We measured daytime blood pressure as the average of two consecutive measurements on the non-dominant arm while seated after a 5 min resting period. We assessed somatic multimorbidity with a self-assessment and a physician-rated questionnaire. The Patient Health Questionnaire Somatic Symptom Scale (PHQ-15) is a self-administered questionnaire measuring the severity of somatic symptoms (e.g., back pain) within the previous four weeks. It is composed of 15 items on a three-point Likert scale (*0 = not bothered at all to 2 = bothered a lot*). This questionnaire covers 90% of physical complaints reported in outpatient settings. Its validity has been demonstrated [90]. We used the Patient Health Questionnaire-9 (PHQ-9) to assess depressive symptom severity [91]. Nine items (e.g., "feeling down, depressed or hopeless") are scored on a four-point Likert scale (*0 = not at all to 3 = nearly every day*). The validity of the cut-offs (mild to severe depression) have been demonstrated [91]. We measured anxiety using the Hospital Anxiety and Depression Scale (HADS) [92]. The anxiety subscale contains seven items (e.g., *"I get sudden feelings of panic."*), each on a four-point Likert scale (e.g., *0 = not at all to 3 = most of the time*). Diagnostic test accuracy and other psychometric properties have been demonstrated [92,93]. We used the Pittsburgh Sleep Quality Index (PSQI) to assess subjective sleep problems [94,95]. Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, the use of sleeping medication, and daytime dysfunction are measured with 18 items. The cut-off value of ≥ 5 has been shown to distinguish good from poor sleepers [96]. We assessed sleep reactivity with the Ford Insomnia Response to Stress Test (FIRST) [97,98]. Sleep reactivity is defined as the likelihood of sleep disturbances in response to stressful situations (e.g.,

"How likely is it for you to have difficulty sleeping after an argument"). There are nine items on a four-point Likert scale (*1 = not very likely* to *4 = very likely*). Its reliability and validity have been demonstrated [99]. Lastly, we administered the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS) [100]. The sixteen items (e.g., *"I am worried that I may lose control over my ability to sleep."*) are rated on a Likert scale (*0 = strongly disagree* to *10 = strongly agree*). The reliability and validity of this questionnaire has been demonstrated [100].

We defined the intensity of the intervention based on the individual anaerobic threshold. Consequently, all patients performed a submaximal graded exercise test on a bicycle ergometer (ergoselect 200, Ergoline, Bitz, Germany) before randomization. We determined the anaerobic threshold according to the method of Dickhuth et al. [101] using a specialized software program (Ergonizer, Freiburg, Germany). A detailed description of the graded exercise testing can be found in the study protocol [84].

2.3. Randomization

We randomized patients once eligibility was confirmed through baseline polysomnography. We used a nondeterministic unweighted minimization algorithm [102] with a random element of 0.8. The allocation ratio was 1:1. We selected sex, age, depression severity (PHQ-9 score), and subjective sleep quality (PSQI score) as minimization factors. We wanted to ensure the baseline balance of these factors because they are potentially associated with insomnia symptoms or moderate the effects of exercise interventions [103–105]. Our allocation concealment consisted of four steps: (1) requesting randomization after baseline measurement, (2) using a random element, (3) requesting randomization by four different study nurses, and (4) not disclosing the full details of minimization to study nurses, in accordance with the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guideline [106].

2.4. Graded Exercise Test, Intervention, and Control

The intervention consisted of a single session of supervised moderate-intensity aerobic exercise on a bicycle ergometer (ergoselect 200, Ergoline, Bitz, Germany). The warm-up period lasted five minutes, with a linear increase from 50% to target intensity. We defined target intensity as 80% of the individual anaerobic threshold (defined by graded exercise testing), i.e., moderate intensity. The duration of the exercise intervention was 30 min. Thereby, the intervention corresponds to the minimum daily physical activity recommendation [107]. We recorded perceived exertion in the 5th, 15th, and 30th minute as well as the average Watt and heart rate (Polar® H7 chest strap, Polar OY, Finland) throughout the intervention. Patients allocated to the control group sat and read magazines when the intervention group was exercising. The exercise and control conditions started at approximately 16:45.

We implemented several procedures to limit the risk of performance bias. Patients were instructed to refrain from moderate or vigorous exercise on the days of the submaximal exercise test, as well as before and after the polysomnographies. In addition, we assessed contamination through other physical activity with accelerometers. All patients wore a validated [108] (vivofit®2, Garmin, Schaffhausen, Switzerland) accelerometer on their non-dominant wrist on the days before and after the polysomnographies. Lastly, the therapy schedule and rules (e.g., timing of meals, consumption of alcohol) of the inpatient rehabilitation clinic limited the variability of many behavioral aspects and ancillary treatments which could influence sleep.

2.5. Baseline and Follow-Up Assessments

Outcome assessments at baseline and follow-up were repeated in an identical fashion. Since we could not blind participants in exercise trials, we used objective and subjective measurements to assess arousal.

2.5.1. Polysomnography and Heart Rate Variability

We performed polysomnography with the SOMNOscreen™ plus RC (Somnomedics, Randersacker, Germany) using the following montage: one EEG channel (Fp2-A1, 512 Hz), two EOG channels (1 cm below and 1 cm lateral of the outer right canthus as well as 1 cm above and 1 cm lateral of the outer left outer canthus, 512 Hz), one EMG channel (Chin1–Chin2, 512 Hz), one ECG channel (below the midpoint of the right clavicle and below the left breast crease, in line with the midpoint of the left clavicle, 512 Hz), a thoracic respiratory effort channel (inductance plethysmography belt, 32 Hz), finger photoplethysmography (non-dominant arm, 128 Hz), body position (stored every 30 s), movement (32 Hz), and ambient light (stored every 30 s). Two trained scorers rated sleep stages independently according to the American Association of Sleep Medicine guidelines [109]. Both scorers demonstrated good agreement with the gold standard ratings in the AASM inter-scorer program [110]. Scorers were blinded against allocation, time point, and each other's ratings. Participants were instructed to lay in bed for at least five more minutes after they woke up.

ECG pre-processing and HRV analysis was carried out while being blinded against allocation and time point using Kubios HRV (Version 3.4.2) (University of Eastern Finland, Kuopio, Finland) [111]. The validity of Kubios HRV has been demonstrated [112]. QRS detection was based on the Pan-Tompkins algorithm [113], including bandpass filtering. Artifacts were identified using a validated algorithm [114]. We visually inspected beat detection, manually adding missed beats when necessary. Ectopic beats were replaced by phantom beats using cubic spline interpolated RR values. Detrending was performed using the smoothness priors approach ($\lambda = 500$, fc = 0.035 Hz) [115]. We computed power spectral density using Lomb–Scargle periodogram (LSP) [116,117] with a moving average filter (width 0.02 Hz). We chose LSP instead of Fast Fourier Transformation (FFT) and autoregressive modeling (AR) for multiple reasons. FFT and AR require resampling (thereby introducing bias [118,119]) and a trade-off between frequency resolution and time resolution [120,121]. LSP, however, makes no assumptions of models, is more accurate [122–124], is less noisy [125], has higher reliability [126], and is more sensitive to physiological changes [125–127] compared to FFT. Based on the aforementioned specifications, we report low-frequency power (LF, 0.04–0.15 Hz [ms2]), high-frequency power (HF, 0.15–0.4 Hz [ms2]), and the LF/HF ratio [128]. Time-domain parameters include the heart rate, the root mean square of successive differences of normal-to-normal intervals (RMSSD), and the standard deviation of all normal-to-normal intervals (SDNN). Although there is an ongoing debate about the physiological correlates of some HRV variables, RMSSD and HF are generally accepted to be measures of vagal modulation [129,130].

We assessed HRV (1) during the last 5 min segment before the first epoch of any sleep stage, (2) during the sleep period (i.e., from the first to the last episode of any sleep stage), and (3) during each sleep stage. The methodological details and the rationale for this choice are presented in Table S1. We excluded any 5 min segment from the analysis which had either $\geq$5% artifacts or in which the patient was upright. Correction for heart rate was not necessary, since the heart rate did not differ between both groups in any of the HRV analyses. Sleep period RMSSD was the primary HRV marker of interest, since it has a clear physiological interpretation in the context of arousal (i.e., vagal tone).

2.5.2. Pre-Sleep Arousal

We asked participants to complete the Pre-Sleep Arousal Scale [131] upon awakening from baseline and follow-up nights. The Pre-Sleep Arousal Scale assesses cognitive (eight items) and somatic (seven items) pre-sleep arousal symptoms. Patients rate how intensely they experienced each of the symptoms as they attempted to fall asleep. All 15 items (e.g., "a jittery, nervous feeling in your body") are scored on a five-point Likert scale (*1 = not at all* to *5 = extremely*) and summed up for each factor separately [131,132].

2.6. Statistical Methods

We examined whether there was a first-night effect in the control group. Since we found no first-night effect, we included baseline and follow-up measures in the analysis using an ANCOVA model [133]. We used baseline outcome and minimization factors [134] as covariates, allocation as the independent variable, and follow-up outcome as the dependent variable. We checked all statistical prerequisites. We computed robust standard errors in the case of heteroscedastic residuals (using HC3) [135]. Predefined sensitivity analyses for the primary outcome of interest (i.e., follow-up RMSSD) were performed to gauge the influence of several factors: influential data points, smoking status, as well as use of beta-blockers, any class of antidepressants, and tricyclic antidepressants. We used multiple imputation with predictive mean matching to replace missing values [136] and conducted intent-to-treat analyses. The missing completely at random assumption was met using Little's test [137]. All analyses were performed using the software R, version 3.6.3 [138].

Sample size calculation was based on another outcome (i.e., sleep efficiency, see study protocol [84] for comprehensive details). We did not perform an a priori or post hoc sample size calculation for secondary outcomes.

3. Results

We screened 448 patients between September 2018 and January 2020. We randomized 92 patients to either the aerobic exercise intervention ($N = 46$) or the control condition ($N = 46$), as shown in Figure 1. Reasons for data loss included dropouts ($N = 2$ in each group), ECG measurement failure ($N = 3$ in the intervention arm), and a patient who removed the polysomnographic equipment during the night ($N = 1$ in the control group). We excluded multiple patients due to ECG abnormalities ($N = 5$ and $N = 4$ in intervention and control arm, respectively). This resulted in $N = 36$ and $N = 39$ complete ECG datasets (i.e., baseline and follow up) for the intervention and control arm, respectively. During the sleep period (sleep onset until the last awakening), the average amount of corrected beats was 0.34% (range: 0.02–2.13%). Baseline characteristics of the study sample are presented in Table 1. As reported previously for this study [87], the inter-rater reliability of polysomnographic scoring was good, and the daily steps during the trial as well as the rate and intensity of adverse events did not differ between the groups.

3.1. Sleep Period

There was no evidence that heart rate differed between the groups during the sleep period ($\beta = -0.43$, 95% CI: −1.44–0.58, $p = 0.40$). The intent-to-treat analysis ANCOVA of follow-up RMSSD, adjusted for pre-intervention levels and minimization factors, did not detect a significant effect of the allocation during the sleep period (see Table 2 and Figure 2). The difference between the mean change scores (baseline to follow up) of both groups corresponds to the coefficient for allocation (see Table 2). This finding was confirmed in all pre-specified sensitivity analyses (i.e., only using complete data, excluding patients who smoked, used either beta-blockers, any antidepressant, or only tricyclic antidepressants). We identified one influential data point using Cook's distance and DFBETAs, but excluding this data point did also not alter the finding.

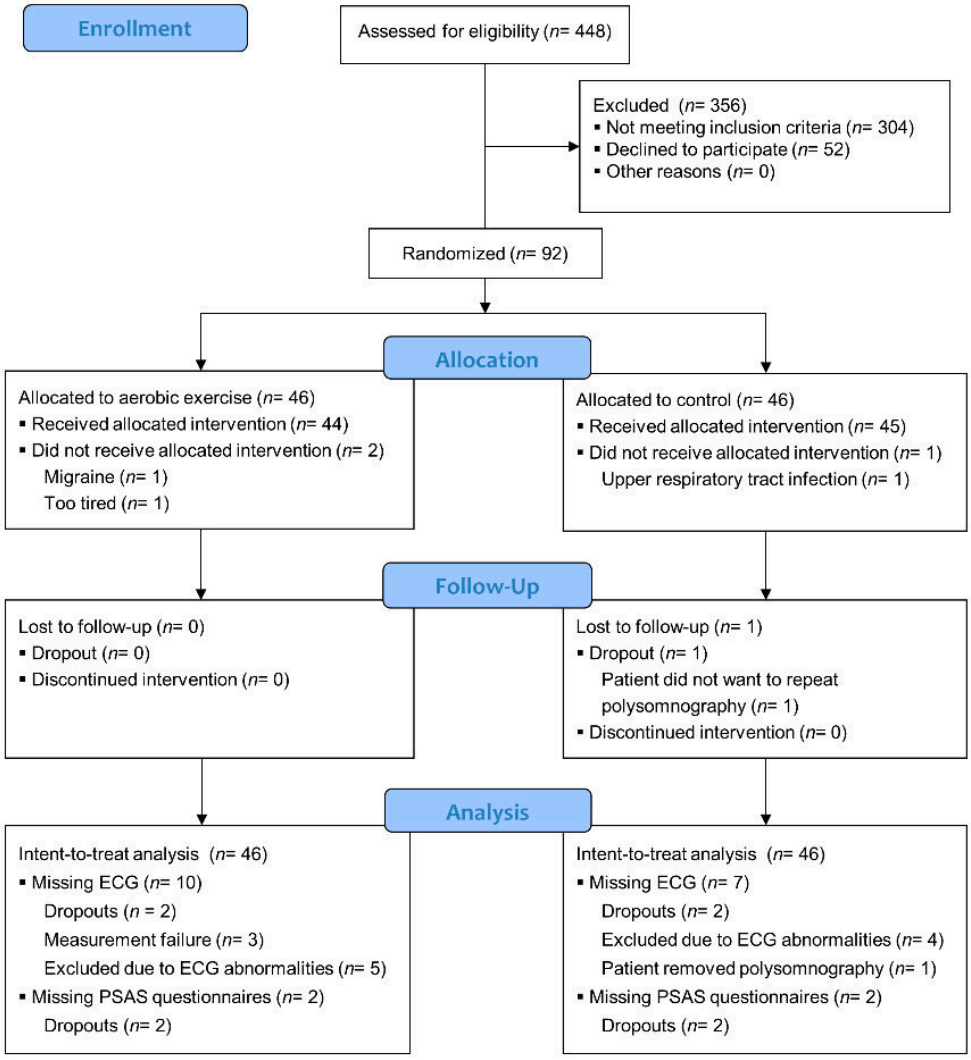

Figure 1. CONSORT participant flow.

Table 1. Baseline characteristics.

		Intervention Group (N = 46)	Control Group (N = 46)
Age		46 (37, 53)	48 (43, 51)
Sex	female	32 (70)	33 (72)
	male	14 (30)	13 (28)
BMI		25.0 (21.8, 29.2)	24.4 (22.2, 27.7)
Systolic blood pressure (mmHg)		121 (115, 131)	121 (112, 134)
Diastolic blood pressure (mmHg)		80 (74, 88)	81 (72, 87)
Smoking	never smoked	26 (57)	24 (52)
	stopped smoking since ≥12 months	8 (17)	10 (22)
	currently smoking or stopped since <12 months	12 (26)	12 (26)

Table 1. *Cont.*

		Intervention Group (*N* = 46)	Control Group (*N* = 46)
Alcohol	less than 1 day/week	5 (15)	6 (18)
	1–2 days/week	14 (41)	6 (18)
	3–6 days/week	7 (21)	12 (37)
	daily	8 (23)	9 (27)
PHQ15		12.5 (8.3, 15.8)	12.5 (8.0, 14.0)
PHQ9		14.0 (12.0, 17.0)	15.0 (12.0, 17.0)
HADS anxiety		11.0 (9.3, 14.0)	11.5 (9.0, 14.0)
Antidepressant medication		19 (41)	21 (50)
DBAS		4.6 (3.6, 5.7)	4.8 (3.8, 5.4)
FIRST		27.0 (24.0, 29.8)	27.5 (21.3, 29.8)
PSQI		10.0 (7.00, 13.8)	9.5 (6.3, 12.0)
Sleep efficiency [a]		91.3 (84.4, 93.5)	88.8 (82.5, 94.0)
Total sleep time [a]		439.0 (393.3, 479.5)	416.7 (382.3, 463.1)
Sleep onset latency [a]		14.0 (5.5, 23.3)	14.5 (6.8, 27.2)
Wake after sleep onset [a]		30.8 (18.0, 43.3)	37.8 (19.1, 62.6)
Number of awakenings [a]		17.0 (13.5, 23.5)	15.8 (11.4, 20.8)
RMSSD		32.1 (20.7, 49.0)	34.4 (24.5, 51.4)
SDNN		37.8 (27.2, 55.0)	34.7 (29.5, 52.6)
LF (ms^2)		858 (474, 1659)	780 (436, 1852)
HF (ms^2)		382 (159, 925)	410 (253, 810)
Somatic pre-sleep arousal		10.0 (9.0, 12.8)	12.0 (9.0, 15.0)
Cognitive pre-sleep arousal		15.0 (13.3, 18.0)	15.0 (11.0, 20.0)

Note: Continuous variables are presented as medians with interquartile ranges (median (Q_1, Q_2)) and categorical variables are presented as absolute numbers and percentages (N (%)). [a] measured polysomnographically. Abbreviations: BMI = body mass index; PHQ15 = Patient Health Questionnaire 15; PHQ9 = Patient Health Questionnaire 9; HADS anxiety: Hospital Anxiety and Depression, anxiety subscale; DBAS = Dysfunctional Beliefs and Attitudes about Sleep Scale; FIRST = Ford Insomnia Response to Stress Test; PSQI = Pittsburgh Sleep Quality Index; RMSSD = root mean square of successive differences between normal heartbeats; SDNN = standard deviation of normal-to-normal RR intervals; LF = low-frequency power (0.04–0.15 Hz (ms^2)); HF = high-frequency power (0.15–0.4 Hz (ms^2)).

Table 2. ANCOVA table for intent-to-treat analysis of RMSSD during sleep period at follow-up.

Term	Estimate (β)	Standard Error (β)	95% Confidence Interval		*p*-Value
Intercept	6.78	6.03	−5.42	18.98	0.27
Baseline RMSSD	0.93	0.04	0.84	0.84	0.001
Age	−0.10	0.10	−0.30	0.10	0.61
Sex (male [a])	1.21	1.70	−2.22	4.64	0.48
PHQ9	0.08	0.17	−0.26	0.42	0.64
PSQI	−0.16	0.18	−0.51	0.19	0.37
Allocation (exercise [b])	0.12	1.53	−2.98	3.22	0.94

Note: age, sex, PHQ9, and PSQI were entered as covariates because they were used as minimization factors. Abbreviations: RMSSD = root mean square of successive differences between normal heartbeats; PHQ9: Patient Health Questionnaire 9; PSQI: Pittsburgh Sleep Quality Index. [a] Sex was coded as follows: 1 = male, 2 = female. [b] Exercise was coded as follows: 1 = control, 2 = exercise.

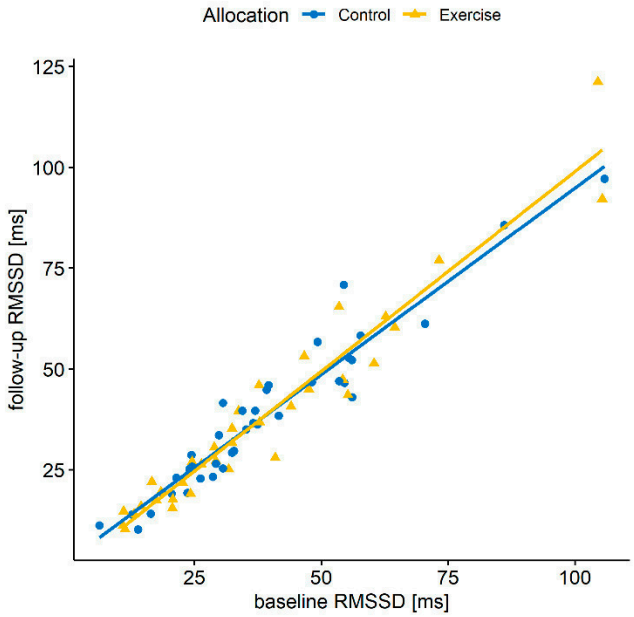

Figure 2. Baseline and follow-up RMSSD by allocation.

There was no evidence that any of the other HRV outcomes were affected through the intervention during the sleep period (see Table 3). Sensitivity analyses based on complete data only, excluding patients who smoked, used either beta-blockers, any antidepressant, or only tricyclic antidepressants, also confirmed these results.

Table 3. Coefficients of exercise allocation in intent-to-treat analysis ANCOVA models predicting HRV outcomes during sleep period.

Outcome	Estimate for Exercise Allocation [a] (β)	Standard Error (β)	95% Confidence Interval		p-Value
SDNN	−0.27	1.78	−4.08	3.53	0.88
LF	−130	260	−791	531	0.64
HF	16	75	−135	167	0.83
LF/HF-ratio	−0.17	0.34	−0.85	0.51	0.62

Note: All models used baseline values of the outcome as well as minimization factors (sex, age, PHQ9 score, and PSQI score) as covariates and allocation as the independent variable. The coefficient for allocation is the difference of the mean change score in the exercise group compared to the control group. Abbreviations: SDNN = standard deviation of normal-to-normal RR intervals; LF = low-frequency power (0.04–0.15 Hz (ms^2)); HF = high-frequency power (0.15–0.4 Hz (ms^2)). [a] Allocation was coded as follows: 1 = control, 2 = exercise.

3.2. Sleep Stages

We found no evidence that heart rate differed during any sleep stage (N2: $\beta = -0.70$, 95% CI: −2.26–0.85, $p = 0.37$; N3: $\beta = -0.21$, 95% CI: −2.64–2.22, $p = 0.86$; non-REM: $\beta = -0.40$, 95% CI: −1.71–0.91, $p = 0.54$; REM: $\beta = -0.40$, 95% CI: −2.47–1.67, $p = 0.70$). There was no evidence that the aerobic exercise intervention affected RMSSD during stage two or stage three sleep, nor during REM or non-REM sleep (see Table 4). Since most patients did not have an uninterrupted 10 min segment of N1 sleep on both nights needed for this analysis, we could not perform the analysis for this stage of sleep.

Table 4. Coefficients of exercise allocation in intent-to-treat ANCOVA models predicting RMSSD outcomes during different sleep stages.

Sleep Stage	Estimate for Exercise Allocation [a] (β)	Standard Error (β)	95% Confidence Interval		p-Value
N2	−0.69	4.75	−10.41	9.02	0.88
N3	−7.15	7.11	−23.10	8.81	0.34
non-REM	0.29	1.81	−3.32	3.90	0.87
REM	−4.93	8.04	−22.42	12.55	0.55

Note: All models used baseline values of the outcome as well as minimization factors (sex, age, PHQ9 score, and PSQI score) as covariates and allocation as the independent variable. The coefficient for allocation is the difference of the mean change score in the exercise group compared to the control group. Abbreviations: N2 = stage two sleep, N3 = stage three sleep, REM = rapid eye movement sleep. [a] Allocation was coded as follows: 1 = control, 2 = exercise.

3.3. Pre-Sleep

We had to exclude seven measurements (N = 4 at baseline, N = 3 at follow-up) in addition to the missing data reported in Figure 1 from this analysis because these segments either had ≥5% artifacts, the patient was upright, or the patient fell asleep within the segment. We did not find any evidence that the intervention altered pre-sleep heart rate (β = 0.53, 95% CI: −3.03–4.08, p = 0.77) or pre-sleep HRV (see Table 5).

Table 5. Coefficients of exercise allocation in intent-to-treat ANCOVA models predicting HRV outcomes during the pre-sleep period.

Outcome	Estimate for Exercise Allocation [a] (β)	Standard Error (β)	95% Confidence Interval		p-Value
RMSSD	0.21	2.61	−4.99	5.41	0.94
SDNN	−1.00	2.58	−6.15	4.15	0.70
LF	34	155	−274	343	0.83
HF	100	130	−158	358	0.44
LF/HF-ratio	1.33	1.05	−0.76	3.43	0.21

Note: All models used baseline values of the outcome as well as minimization factors (sex, age, PHQ9 score, and PSQI score) as covariates and allocation as the independent variable. The coefficient for allocation is the difference of the mean change score in the exercise group compared to the control group. Abbreviations: RMSSD = root mean square of successive differences between normal heartbeats; SDNN = standard deviation of normal-to-normal RR intervals; LF = low-frequency power (0.04–0.15 Hz (ms^2)); HF = high-frequency power (0.15–0.4 Hz (ms^2)). [a] Allocation was coded as follows: 1 = control, 2 = exercise.

Cronbach's α of the cognitive (baseline = 0.87; follow up = 0.90) and somatic (baseline = 0.71; follow up = 0.78) pre-sleep arousal subscales were good. Intent-to-treat ANCOVAs of follow-up pre-sleep arousal, adjusted for baseline levels and minimization factors, also provided no evidence that the intervention altered somatic (β = −0.65, 95% CI: −2.04–0.74, p = 0.35) or cognitive (β = −0.15, 95% CI: −2.08–1.79, p = 0.88) pre-sleep arousal.

4. Discussion

The primary goal of this trial was to quantify the effect of a single bout of 30 min moderate aerobic exercise on arousal measured by HRV during sleep in patients with depression. We did not find evidence that the intervention affected HRV during the sleep period, nor in specific sleep stages. The absence of evidence was very robust. The findings were confirmed across all outcome measures of HRV and in all of the sensitivity analyses.

To the best of our knowledge, this is the first trial to investigate the effects of a single bout of aerobic exercise on arousal measured by HRV during sleep in patients with depression. Trials in primarily young and healthy individuals have found mixed results. There are diverging findings concerning the duration of an exercise intervention on HRV in the subsequent night. Myllymäki et al. [139] found that an incremental bicycle ergometer exercise until exhaustion lasting approximately 30 min did not alter HRV. This was confirmed by another study, which showed that moderate-intensity aerobic exercise

sessions lasting 30 or 60 min had no effect, while sessions of 90 min decreased nocturnal HRV [75]. Trials concerning the effect of exercise intensity have also produced inconsistent results. Except for one study [82], multiple [75–81] trials found no evidence that moderate-intensity exercise altered HRV during the night. Five trials that directly compared moderate and vigorous exercise intensities on nocturnal HRV found no difference [75–79], whereas two trials found that high-intensity exercise reduced nocturnal HRV [80,81]. Another two trials only comparing high-intensity exercise with a control condition also found that the intervention reduced nocturnal HRV [79,140]. The effects of exercise timing during the day are equally inconclusive. In healthy young males, exercising vigorously on three consecutive days in the morning altered HRV (increasing LF and HF) outcomes during sleep, but exercising in the evening did not have a discernable effect [141]. However, Ramos-Campo et al. [77] found no evidence that morning or evening exercise affected HRV during sleep in trained individuals. However, prolonged and intense exercise such as a marathon [82] or a 75 km cross-country skiing race [142] have been shown to reduce HRV during the following night. Many of these trials investigating the acute effects of exercise on sleep were conducted with trained or healthy individuals. HRV in athletes tends to be higher [143], whereas in patients with unipolar depression, HRV tends to be lower [30] compared with healthy controls. This should be taken into account when interpreting these results. Acute effects of aerobic exercise on HRV during sleep might depend on exercise variables such as intensity, duration, volume, and timing during the day, as well as the training status of study participants. Our results are in line with the findings presented above, i.e., there is no evidence that a single moderate aerobic exercise session of 30 min performed multiple hours before bedtime is a strong enough stimulus to alter HRV in the subsequent night. All of these trials analyzed nocturnal HRV in fixed periods without accounting for the different sleep phases.

We are aware of only one other trial which analyzed the acute effects of aerobic exercise on HRV during different sleep phases. Yamanaka et al. [141] subjected healthy young males to a 7-day dim light (<10 lux) protocol. Subjects performed vigorous-intensity aerobic exercise during the morning or afternoon on three consecutive days for 90 min each day (10 min of warming up, 45 min of exercise, 10 min of rest on a chair, 45 min of exercise, and 10 min of cooling down). After three days, the morning group had higher values in LF and HF during N1 and N2 as well as higher values in HF during N3. We did not find any evidence that the intervention altered HRV during sleep stages N2 and N3, as well as non-REM and REM sleep. However, sleep stage N1 could not be analyzed. Possible reasons for theses diverging findings might be the dim light setting, the repeated exercise stimulus over three days, and the specification of exercise variables (90 min at vigorous intensity).

We did not find evidence that a single bout of moderate-intensity aerobic exercise altered objectively or subjectively measured pre-sleep arousal. We did not detect an effect of the intervention on any of the HRV indices measured in the last 5 min before the first epoch of sleep. Furthermore, there is no evidence to suggest that the somatic or cognitive pre-sleep arousal questionnaire subscales differed between the groups. This is the first trial to investigate the effect of aerobic exercise on pre-sleep arousal in patients with depression or any other group of participants, to the best of our knowledge.

Oda and Shirakawa [76] investigated the acute effects of aerobic exercise on 'emotional comfort' before falling asleep—an outcome potentially similar to pre-sleep arousal. An amount of 40 min of moderate or vigorous exercise (ending one hour before going to bed) led to higher 'emotional comfort' compared to the control condition. Although the construct of 'emotional comfort' might be related to pre-sleep arousal, these findings are not transferable to clinical populations because the trial only included healthy participants. Theoretical considerations and data from previous trials suggest that reducing pre-sleep arousal, as measured by HRV, might be beneficial in people with insomnia symptoms. Guidelines recommend cognitive behavioral therapy for insomnia as a first-line therapy [144], to, amongst other effects, reduce pre-sleep arousal [145]. There is some evidence that biofeed-

back interventions that reduce pre-sleep arousal positively affect cardiac autonomic control during the night [146,147] and objectively measured sleep quality [147,148].

These findings have implications for clinical practice and research. While our results do not suggest that a single session of moderate-intensity aerobic exercise ameliorates nocturnal HRV, they are in line with previous studies which failed to detect a negative effect on nocturnal HRV. This contradicts the current sleep hygiene recommendations [74]. These recommendations state that rigorous exercise might release endorphins, thereby hindering sleep onset [74]. The evidence from our study suggests that moderate-intensity aerobic exercise after 2 pm can be cautiously recommended as far as autonomic, cognitive, and somatic arousal are concerned. Moreover, previous trials in healthy individuals found no adverse effects on sleep from an acute exercise bout in the evening [149]. Considering that arousal might be a common pathophysiological mechanism in insomnia and depression and the paucity of literature concerning interventions that can reduce arousal, future studies are needed. Such trials should try to identify interventions that can reduce arousal, e.g., biofeedback or mindfulness-based stress reduction. Trials specifically investigating exercise should focus on the effect that intensity, duration, and timing have on HRV or other measures of arousal. More broadly, HRV has been recognized as an index of self-regulation [150] and as a transdiagnostic biomarker of psychopathology [151]. Hence, in future studies, it would be interesting to study the effects of exercise on HRV in the context of self-regulation and interoception [152].

This study has several strengths and limitations. The risk of bias was limited through multiple procedures: allocating patients using minimization with appropriate allocation concealment (selection bias), blinding outcome assessors during polysomnography rating and HRV data analysis (detection bias), avoiding contamination through other physical activity and extraneous factors (performance bias), and using intent-to-treat analysis (attrition bias). However, the external validity of this trial might be limited by two factors: the exclusion of patients who used hypnotics (although this increases internal validity) and the relatively normal levels of polysomnographically measured sleep variables (see Table 1). Both these factors may not be representative of typical patients with depression. The a priori sample size calculation for this study was not calculated for sleep period RMSSD, but for another outcome which we have reported elsewhere [87]. Lastly, the menstrual cycle was not considered as a potentially confounding variable. However, it seems unlikely that this factor has influenced the results since the duration of the trial was very short (i.e., measurements were conducted on two consecutive nights) and the statistical analyses adjusted for baseline values. However, we cannot definitively exclude the possibility that the menstrual cycle may have influenced susceptibility to exercise-induced HRV changes.

5. Conclusions

We found no evidence that a single 30 min bout of moderate-intensity aerobic exercise affected pre-sleep or nocturnal arousal reflected by indices of HRV. Our findings need to be interpreted cautiously, considering that this is the first trial of this nature in patients with depression. The evidence base remains insufficient to explicitly recommend exercising in the late afternoon or evening hours to ameliorate sleep. Non-inferiority trials and studies investigating the interplay of exercise intensity, duration, and timing, with patient characteristics (e.g., chronotype) are needed. This would further our understanding, allowing for the formulation of personalized exercise prescriptions.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10174028/s1, Table S1: Time spans for which HRV was calculated and the rationale.

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Supplementary

Table S1. Time spans for which HRV was calculated and the rationale.

Time span	Operationalization	Rationale
Pre-sleep	The 5-minute segment before the first epoch of any sleep stage	Theoretical considerations [1,2] and empirical data suggest that reducing pre-sleep arousal can ameliorate sleep [3–5].
Sleep period	The average of consecutive non-overlapping 5-min segments starting from the beginning of the first epoch of sleep to the end of the last epoch of sleep (i.e., including periods of wakefulness)	Depression is associated with lower HRV during the night [6–10].
Sleep stages N1, N2, N3, and REM	Only 5-min segments consisting of consecutive epochs of a particular sleep stage (N1, N2, N3, or REM) were included in the analysis. The last consecutive 5-minute segment of a particular sleep stage was excluded since changes in HRV have been shown to precede sleep stage changes [11–14]. Hence, only phases containing at least 10 minutes with consecutive epochs of a particular sleep stage were used to extract 5-min segments for the analysis. We computed the average of all 5-min segments for each sleep stage. This is analogous to the method used by Herzig et al. 2018 [15].	We differentiate individual sleep stages as well as non-REM and REM sleep since these sleep stages also differ in terms of parasympathetic and sympathetic predominance [14].

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Chapter 8

Discussion

8 Discussion

The discussion is structured in seven parts. First, a summary of the results regarding the hypotheses raised in Chapter 2 is provided. Second, the results are discussed within the state of science. Third, potential mechanisms of action which might explain the effect of exercise on sleep are summarized. Fourth, strengths and weaknesses of the Ph.D. project are delineated. Fifth, clinical implications are highlighted. Sixth, future avenues of research are outlined. Lastly, this chapter closes with concluding remarks.

8.1 Synopsis

Hypothesis 1: Aerobic, resistance, and mind-body exercise improve insomnia symptoms and subjective sleep quality in patients with unipolar depression.

Publication 2 [1] showed that all exercise types and intensity levels except moderate aerobic exercise (SMD: -0.31; 95% CI: -0.62, 0.00) were more efficacious than passive control at improving sleep quality. The point estimates for active control (SMD: -0.44; 95% CI: -0.76, -0.12), mind-body exercise (SMD: -0.44; 95% CI: -0.65, -0.24), treatment as usual (SMD: -0.48; 95% CI: -0.75, -0.22), and vigorous aerobic exercise (SMD: -0.50; 95% CI: -0.81, -0.19), resulted in similar effects. Augmenting treatment as usual with either moderate (SMD: -0.56; 95% CI: -1.11, -0.02) or vigorous aerobic (SMD: -0.66; 95% CI: -1.09, -0.23) exercise lead to somewhat larger effect sizes, but these differences were not statistically significant. Augmenting treatment as usual with mind-body exercise, on the other hand, significantly increased the point estimate (SMD: -0.94; 95% CI: -1.35, -0.54). Vigorous strength exercise yielded the largest effect on sleep quality compared to passive control (SMD: -1.09; 95% CI: -1.64, -0.55). This effect was not significantly larger compared to light strength exercise (SMD: -0.63; 95% CI: -1.12, -0.14), but larger than aerobic or mind-body exercise.

Mind-body exercise combined with treatment as usual (SMD: -0.46; 95% CI: -0.80, -0.12) and vigorous strength (SMD: -0.61; 95% CI: -1.12, -0.10) improved sleep quality significantly more than treatment as usual. None of the exercise modes or intensities was significantly less efficacious than treatment as usual. Although combining moderate and vigorous aerobic exercise with treatment as usual trended to increase the point size estimate, this difference was not significant.

Table 1: Summary of findings from publication 2.

	Aerobic	**Resistance**	**Mind-body**
Light		LR ↔ Passive control LR ↔ TAU	MB ↑ Passive control MB + TAU ↑ Passive control MB ↔ TAU MB + TAU ↑ TAU
Moderate	MAE ↔ Passive control MAE + TAU ↑ Passive control MAE ↔ TAU		
Vigorous	VAE ↑ Passive control VAE + TAU ↑ Passive control VAE ↔ TAU	VR ↑ Passive control VR ↑ TAU	

Abbreviations: MAE, moderate aerobic exercise; VAE, vigorous aerobic exercise; LR, light resistance exercise; VR, vigorous resistance exercise; MB, mind-body exercise; TAU, treatment as usual
↑, ↓, and ↔: is more, less, or neither more or less efficacious than

Hypothesis 2: An acute bout of moderate-intensity aerobic exercise improves objectively and subjectively measured sleep outcomes in patients with unipolar depression.

Publication 4 [2] provided no evidence for an effect of allocation on sleep efficiency (β = -0.93, 95% CI = -4.32 to 2.47), which was confirmed in all sensitivity analyses (i.e., complete case and per-protocol analysis as well as excluding an influential data point). There was no evidence for a significant interaction effect of chronotype (β = 0.20, 95% CI = -0.08 to 0.47, p = 0.19), expectancy (β = -2.33, 95% CI = -8.43 to 3.79, *p* = 0.45), and credibility (β = -4.17, 95% CI = -12.54 to 4.19, *p* = 0.32). Furthermore, exercise intensity (i.e., rate of perceived exertion and percent of maximal age-predicted heart rate) in the intervention group was not associated with sleep efficiency. There was no evidence for an effect of allocation on any other objective or subjective measure of sleep nor daytime sleepiness.

Hypothesis 3: An acute bout of moderate-intensity aerobic exercise improves mood and does not increase adverse effects in patients with unipolar depression.

Allocation improved mood strongly and consistently across subscales, according to publication 4 [2]. Patients allocated to the intervention group had higher levels of activation (β = 0.85, 95% CI: 0.52 to 1.19), elation (β = 0.59, 95% CI: 0.36 to 0.82), and calmness (β = 0.49, 95% CI: 0.24 to 0.75), as well as less agitation (β = -0.48, 95% CI: -0.85 to -0.12), depressiveness (β = -0.40, 95% CI: -0.66 to -0.14), fatigue (β = -0.91, 95% CI: -1.13 to -0.45), and anger (β = -0.26, 95% CI: −0.51 to −0.01) immediately after the intervention. There was no evidence that allocation affected adverse outcomes. However, there was a trend toward lower symptom severity in the intervention group compared to the control group (*r* = 0.19, *p* = 0.08) immediately post-exercise.

Hypothesis 4: An acute bout of moderate-intensity aerobic exercise does not increase nocturnal and pre-sleep arousal in patients with unipolar depression.

Publication 5 [3] provided no evidence that RMSSD differed between the groups during the sleep period (β = 0.12, 95% CI: -2.98 to 3.22). All sensitivity analyses confirmed this finding. Furthermore, no evidence was found that allocation affected RMSSD in any sleep stage (except for N1 due to insufficient data). There was also no evidence to suggest that any of the other HRV parameters (i.e., SDNN, LF, HF, LF/HF-ratio) were affected by allocation during the sleep period. No evidence indicated that allocation altered pre-sleep RMSSD (β = -0.21, 95% CI: -4.99 – 5.41) or pre-sleep somatic (β = -0.65, 95% CI: -2.04 – 0.74, p=0.35) and cognitive (β = -0.15, 95% CI: -2.08 – 1.79, p=0.88) arousal.

Table 2: Summary of findings from publications 4 and 5.

Subjective sleep	Objective sleep	Daytime sleepiness	Mood	Pre-sleep arousal	Nocturnal HRV	Adverse effects
↔	↔	↔	↑	↔	↔	↔

Abbreviations: HRV, heart rate variability

↑: significant improvement through 30 minutes of moderate-intensity aerobic exercise

↔: no evidence for an effect of 30 minutes of moderate-intensity aerobic exercise

The Ph.D. candidate was first and corresponding author in all five publications presented in this Ph.D. thesis. The Ph.D. candidate designed and managed both projects (systematic review with network meta-analysis and randomized controlled trial). Lastly, the Ph.D. candidate performed the analyses and wrote the manuscripts. Details of the contributions of all co-authors are presented in the individual publications.

8.2 General discussion

8.2.1 Effect of regular exercise on sleep in patients with depression

The findings of publication 2 [1] are in line with the majority of previous findings. Most previous meta-analyses of mind-body exercises for healthy and clinical populations revealed similar effect sizes as publication 2 [4–8]. However, Du et al. [9], Li et al. [10], and Jiang et al. [11] reported larger effect sizes. The discrepancies with publication 2 [1] may be explained by the old age of the included participants (Du et al. [9] and Li et al. [10]) and the inclusion of trials reported in Chinese (Jiang et al. [11]). The meta-analysis of Takemura et al. [12] showed a smaller effect size but only included patients with cancer. Compared to previous meta-analyses on aerobic exercise in healthy and most clinical populations [8, 13, 14], the effect sizes in publication 2 [1] are comparable, albeit somewhat smaller. Aerobic exercise resulted in smaller effect sizes in patients with cancer (as seen with mind-body exercise) [12]. A previous review of resistance exercise on sleep which included heterogeneous populations showed slightly smaller effect sizes [15] than publication 2 [1]. Meta-analyses that did not differentiate exercise type [8, 14, 16–20] generally found similar effect size estimates with one notable exception. Mercier et al. [21] only included patients with cancer and discovered no evidence exercise affected sleep. In summary, the effects of exercise on sleep in patients with depression are comparable to those in healthy and clinical populations, with the notable exception of cancer.

The search for moderator variables is a valuable aspect of meta-analyses. The meta-analytic review of Kredlow et al. [18] has shown that intervention-related (exercise type, time of day, duration, and adherence) variables can moderate the effects of aerobic exercise on sleep in healthy individuals. Similarly, the review of Kovacevic et al. [15] showed that high-intensity resistance exercise yielded larger effect sizes compared with low-to-moderate intensity. These findings are partially mirrored by publication 2 [1]. In both aerobic and strength exercises, increasing the intensity tended to generate larger effect sizes, although these differences were non-significant. However, vigorous strength exercise yielded a significantly larger effect than vigorous or moderate aerobic and mind-body exercises in patients with depression. The aggregated data in publication 2 [1] was insufficient to investigate further exercise-related moderators of interest (e.g., expectancy, credibility, time of day, exercise volume, adherence, baseline physical activity level, and baseline cardiorespiratory fitness).

Previous meta-analyses in healthy individuals [18] and people with insomnia [22] suggest that age, sex, or baseline physical activity might alter the effect of exercise on sleep. In publication 2 [1], some of the effect sizes substantially increased in the sensitivity analysis restricted to trials which only included patients with a formal diagnosis of depression. No further patient-related moderator analyses were possible, which avoided ecological fallacy [23].

The review of Mura et al. [24] has shown the efficacy of exercise as an add-on treatment to improve depressive symptoms. Publication 2 [1] extends these previous findings to sleep quality in patients with depression. Combining mind-body exercise with treatment as usual was significantly more efficacious than mind-body exercise alone or treatment as usual alone. Although adding moderate and

vigorous aerobic exercise to treatment as usual increased effect sizes, these differences did not reach statistical significance. These findings are especially pertinent for clinicians.

8.2.2 Acute effects of exercise on sleep in patients with depression

Publication 4 [2] was the first trial to explore the effect of exercise on objectively and subjectively measured sleep in patients with depression, to the author's best knowledge. The absence of evidence for an effect of allocation was consistent across all sensitivity analyses, including patients with hypersomnia symptoms (see appendix 9.1.1). Previous trials investigating the acute effects of exercise in healthy populations or patients with insomnia have focused on objective outcomes. Based on the meta-analytic results of Kredlow et al. [18], acute exercise leads to a reduction of N1 and REM sleep and an increase in slow-wave sleep in healthy individuals. Kredlow et al. also concluded that a moderating effect of exercise duration [18]. Acute aerobic exercise interventions have produced mixed results in patients with insomnia. No changes in objectively measured sleep were seen in two trials [25, 26], whereas some positive effects were observed in three trials [27–29]. Due to the limited number of trials, no clear inferences on exercise intensity or timing can be drawn. However, the aerobic exercise interventions that did elicit significant positive effects lasted 40 or 50 minutes. These results and the findings of Kredlow et al. concerning the moderating effect of exercise duration [18] suggest that 30 minutes (as implemented in publication 4) [2] was insufficient to elicit significant effects on sleep.

Implementing the exercise intervention after 02:00 pm – as explicitly *not* recommended by sleep hygiene guidelines [30] – is unlikely to explain the non-significant finding. Both meta-analyses of Kredlow et al. [18] and Stutz et al. [31] show that exercise after 02:00 pm can positively affect sleep in healthy individuals. Furthermore, it is questionable which mechanisms might explain such an effect. HRV [32] and body temperature [33] will return to baseline within five hours (i.e., until bedtime) after 30 minutes of moderate aerobic exercise.

8.2.3 Acute effects of exercise on mood and adverse events in patients with depression

Negative mood states decreased and positive mood states increased consistently across all subscales after exercise (see appendix 9.1.2). However, these changed in mood were not associated with sleep outcomes (see appendix 9.1.3). The immediate positive effect of exercise on mood shown in publication 4 [2] is consistent with previous findings in patients with depression. All preceding trials found at least some positive effects on mood. Two trials operationalizing mood with multi-dimensional questionnaires revealed an increase in positive and a concurrent decrease in negative mood states [34, 35]. Other trials showed an improvement in some (but not all) of the mood subscales [36–39]. Lastly, Brand et al. [40] and Stanton et al. [41] demonstrated the positive effect of an acute exercise bout on mood using a single-item scale. The discrepancies of the findings above are most likely explained by the differences in sample sizes (with corresponding *p*-values) and questionnaires (assessing different aspects of mood).

Publication 4 [2] was the first trial to investigate and report the adverse effects of acute aerobic exercise in patients with depression, to the author's best knowledge. Although adverse effects are an essential aspect of treatment selection in insomnia [42], they are underreported in exercise [43] and sleep [42] trials. Previous trials on acute adverse effects of aerobic exercise in other populations have focused on sudden cardiac death and acute myocardial infarction [44]. CV events are also a pertinent

issue for patients with depression, considering their increased cardiovascular susceptibility. Although publication 4 [2] did not aim to investigate the risk of cardiac events (sample size was far too small), cardiovascular symptoms were assessed. Immediately after the intervention, the exercise group reported somewhat lower severity of cardiac symptoms (mean = 0.16, SD = 0.37) compared to the control group (mean = 0.37, SD = 0.68), although this difference was not statistically significant, $t(70.9) = 1.8$, $p = 0.08$, $d = 0.37$, see also appendix 9.1.4.

8.2.4 Acute effects of exercise on pre-sleep and nocturnal arousal in patients with depression

Publication 5 [3] was the first trial to examine the effect of exercise on nocturnal arousal in patients with depression, to the author's best knowledge. The findings of publication 5 [3] agree with previous trials that studied the effects of 30 minutes of moderate-intensity aerobic exercise on sleep. These trials also detected no evidence of altered nocturnal HRV in healthy individuals [45–48]. Trials which discovered evidence for lower nocturnal HRV investigated longer sessions (>50 minutes) [46, 49], higher intensities [47, 48, 50], or a combination of both [49, 51]. The effect of exercise on HRV during sleep phases has only been studied in one other trial, to the author's best knowledge. Yamanaka et al. [52] found that 90 minutes of vigorous-intensity aerobic exercise over three consecutive days in a dim-light setting altered HRV during non-REM sleep. The duration, intensity, and repetitive exercise stimulus over three consecutive days and the dim-light setting most probably explain the discrepancy between these findings and publication 5 [3].

Publication 5 [3] was also the first trial to examine the effect of exercise on subjectively and objectively measured pre-sleep arousal, to the author's best knowledge. Other trials have demonstrated that pre-sleep arousal can be attenuated with CBT-I [53] and biofeedback [54–56], thereby improving sleep quality.

8.3 Mechanisms of action

The primary focus of this section lies on the mechanisms of action that might explain the effect of acute and chronic exercise on sleep in patients with depression. Physiological pathways that potentially explain the effects of exercise on the secondary outcomes of mood and arousal are also discussed, albeit in less detail. The putative mechanisms presented below are based on data from in vitro, animal, and human trials (often involving healthy individuals). Exercise might elicit effects by directly acting on the central nervous system. Exercise also stimulates the secretion of molecules in peripheral organs that can pass the blood-brain barrier and transduce central somnogenic effects (see Figure 1).

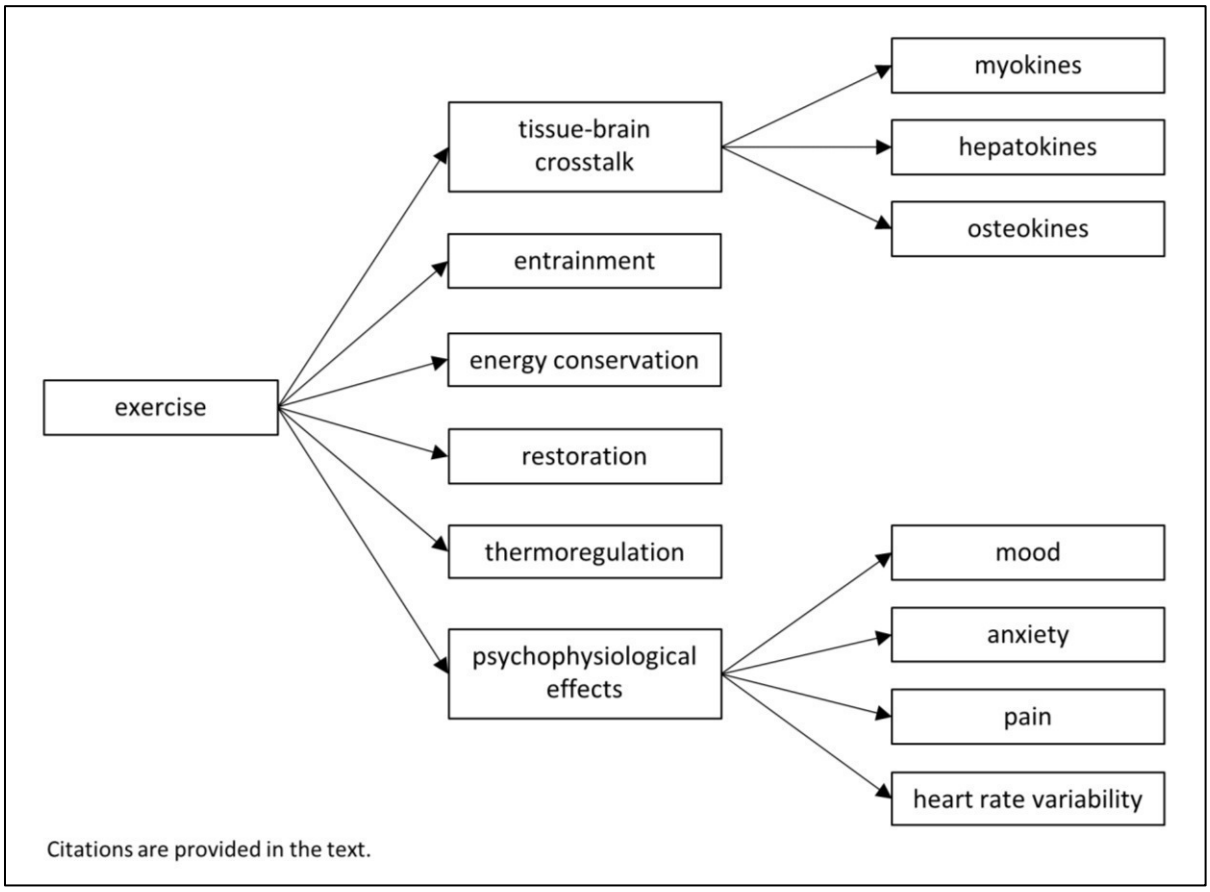

Figure 1: Potential mechanisms of action of exercise on sleep in depression.

8.3.1 Acute effects on sleep

8.3.1.1 Restoration and energy conservation

Although it is not fully understood why humans sleep, it has been hypothesized that humans sleep to conserve energy and optimize restorative processes [57, 58]. Exercise increases energy expenditure and requires muscle repair, thus stimulating such energy-conserving and restorative processes. Indeed, growth hormone secretion is strongest during the first half of the night, especially during slow-wave sleep [59]. Daytime exercise increases the nocturnal release of growth hormone [60]. However, to date, the evidence does not support the hypothesis that the acute exercise-induced nocturnal secretion of growth hormone correlates with changes in sleep quality [60, 61].

8.3.1.2 Thermoregulation

Thermoregulation is a physiological prerequisite for sleep. Sleep onset occurs proximal to the maximal decline in core body temperature mediated by vasodilation in distal skin regions [62–64]. The circadian rhythm of core body temperature is also mainly regulated through heat dissipation by altering the vascular tone of the limbs [65]. Insomnia [66, 67] and depression [68–70] are, however, associated with impaired thermoregulation. Acute aerobic [71], resistance [72], and mind-body exercise [73] increase skin temperature. Exogenously induced nocturnal increase in skin temperature is conducive to sleep [74]. Increased skin temperatures and sleep are associated with similar midbrain reticular formation, hypothalamus, and cerebral cortex activation, which might explain this effect [75].

The exercise-induced increase in skin temperature is transient. Therefore, the only exercise performed close to bedtime might elicit beneficial effects on sleep via thermoregulatory circuits. Interestingly, thermoregulatory reflexes (i.e., increased cutaneous blood flow and sweating) are more efficient in the evening (i.e., during the endogenous fall of core body temperature) compared to the morning (during the rise of core body temperature) in healthy individuals [76–79]. Aritake-Okada et al. [80] have shown that exercise increases core body temperature and distal-proximal skin temperature gradient (i.e., a measure of blood flow in distal skin regions and indirect index of distal heat loss) during sleep. Moreover, the nocturnal distal-proximal skin temperature gradient was correlated with slow-wave activity [80]. However, in two other trials, exercise-induced increases in bedtime and nocturnal core body temperature did not alter sleep quality in healthy males [52, 81].

8.3.1.3 Psychophysiological effects

Acute exercise incudes a variety of beneficial psychophysiological effects on mood, pain, and anxiety. A single bout of moderate aerobic exercise improves mood in patients with depression, as shown in publication 4 [2] and confirmed by other studies [38, 82]. This effect might be explained through multiple pathways. 30 minutes of moderate-intensity aerobic exercise has been shown to reduce stress reactivity and increase positive mood, potentially through decreased prefrontal cortex activity [83]. Acute exercise also increases norepinephrine, dopamine, and serotonin levels [84]. The latter might be modulated by increases in brain-derived neurotrophic factor (BDNF) levels in the brain (see section 8.3.1.5), since BDNF increases serotonergic transmission [85, 86]. Sustained improvements in mood might be elucidated by a reduction in REM sleep (as shown in healthy individuals [18]). REM-sleep is elevated in patients with depression [87] and predicts occurrence, treatment response, and relapse [88]. Moreover, exercise-induced mood improvements are associated with the release of endocannabinoids [82]. Endocannabinoids might also explain the hypoalgesic effect of exercise seen in healthy individuals [89]. Although the trend did not reach significance (p = 0.08), publication 4 [2] indicated a lower somatic symptom severity in the intervention group immediately post-exercise. Lastly, a single bout of aerobic, resistance, and mind-body exercises (especially yoga) also reduces anxiety [90, 91]. These factors could contribute to lower psychophysiological arousal, thus improving sleep. Diurnal timing and the duration for which these acute psychophysiological effects persist are likely to moderate the effect of exercise on sleep.

8.3.1.4 Entrainment

There is clear evidence that exercise acts as a ‘zeitgeber’ (i.e., an external signal that synchronizes physiological 24-hour periodicity) [92]. The exercise phase-response curve (i.e., direction and magnitude of circadian phase shifts) has recently been described by Youngstedt et al. [93]. Exercising

in the early morning (07:00 am) and early afternoon (01:00-04:00 pm) results in a phase advance, whereas exercising in the evening (07:00-10:00 pm) results in a phase delay [93]. Phase-shifting effects of exercise seem to be preserved across the lifespan [94]. However, Thomas et al. [95] revealed that the exercise-induced circadian phase shifts depend on the chronotype. Later chronotypes experienced phase advances from both morning and evening exercise, but earlier chronotypes experienced phase advances from morning exercise and phase delays from evening exercise [95].

The entrainment effect of exercise might partially be explained by Brain and Muscle ARNT-Like 1 (*Bmal1)*, a transcription factor and orchestrator of the molecular clock. *Bmal1* expression in *skeletal muscle* is necessary for normal sleep regulation in the mouse model (whereas *Bmal1* expression in the brain is not) [96]. Exercise increases the expression of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) [97, 98]. PGC1-α, in turn, promotes the expression of *Bmal1* in skeletal muscle cells [99]. Therefore, the zeitgeber effect of exercise might improve the circadian dysregulation associated with depression [100], thus improving sleep.

8.3.1.5 Tissue-brain crosstalk

Muscle-derived interleukin-6

Skeletal muscle cells coordinate exercise adaptation in other organs such as the liver, fat, and brain through myokines [101]. Interleukin (IL)-6 is a myokine involved in metabolic, anti-inflammatory, anabolic, and neural processes and tumor growth [102, 103]. The basal secretion of interleukin IL-6 from skeletal myotubes follows a circadian rhythm and a disruption of the autonomous circadian clock strongly reduces IL-6 secretion [104]. On the other hand, aerobic exercise increases IL-6 levels. Exercise increases IL-6 in a (duration and intensity) dose-dependent manner, with peripheral levels increasing up to 100-fold [105]. Exercise-induced IL-6 secretion is stimulated by lactate-dependent protease activity [106] and osteocalcin, an osteoblast-secreted hormone [107]. Animal and human data show that IL-6 can pass the blood-brain barrier, although enzymatic degradation substantially reduces IL-6 levels in the brain [108, 109].

IL-6 is involved in sleep regulation. Nasal administration of IL-6 increases slow-wave activity in the second half of the night and improves sleep continuity (number of awakenings and sleep efficiency) and recall of emotional text material in healthy individuals [110]. Data from a transgenetic mouse model shows that blocking IL-6 trans-signaling in the body periphery suppresses sleep [111]. Moreover, the exercise-induced secretion of IL-6 from skeletal muscle stimulates the release of Interleukin-1 receptor antagonist (IL-1ra) into the blood [112]. IL-1ra increases slow-wave activity during non-REM sleep and reduces cortisol during sleep in healthy individuals [113]. Therefore, IL-6 might be a mediator linking skeletal muscle cells and sleep-regulating centers in the brain, see Figure 2.

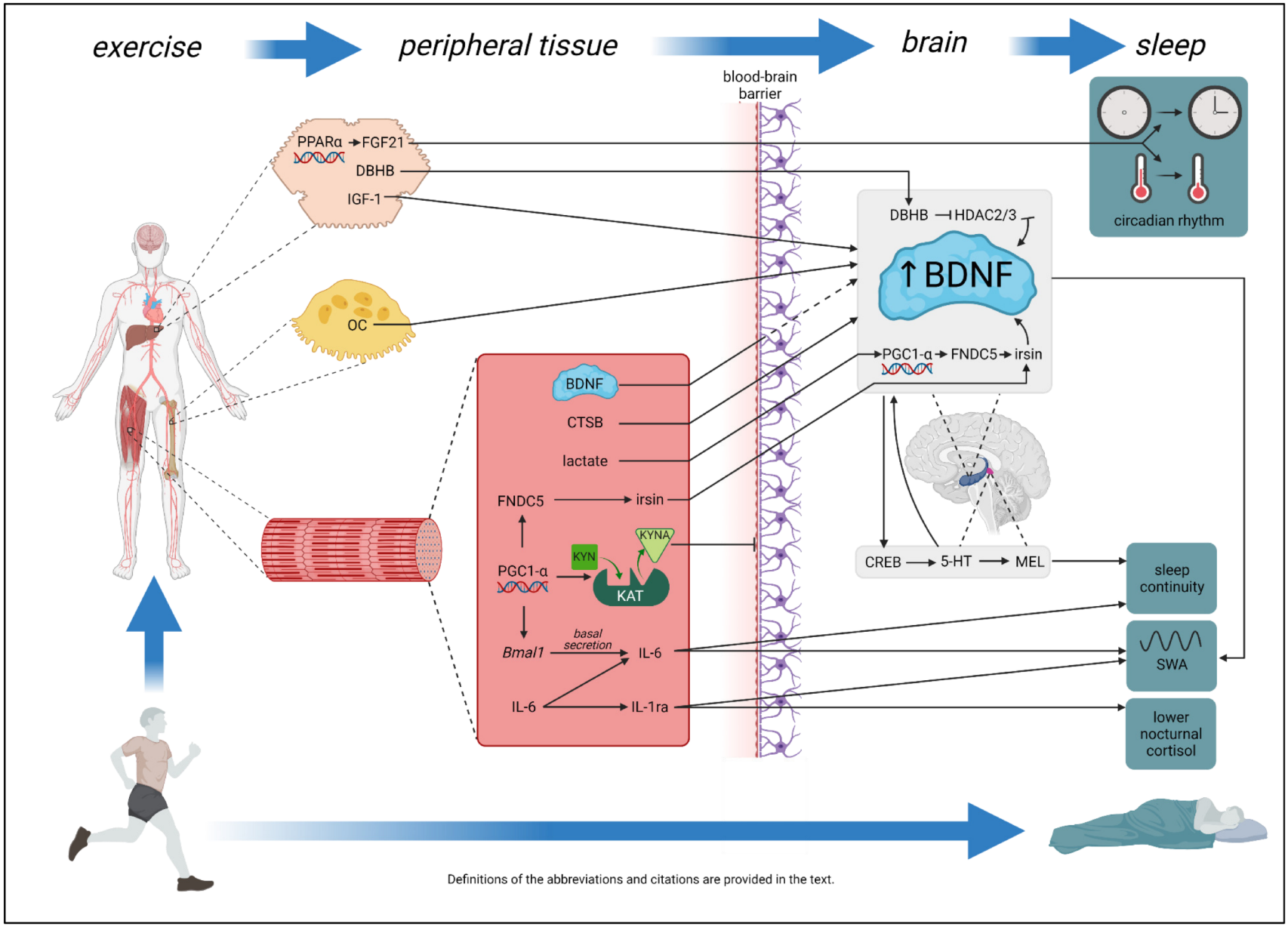

Figure 2: Tissue-brain crosstalk pathways that might explain the effects of exercise on sleep.

Brain-derived neurotrophic factor

A single bout of aerobic exercise transiently increases peripheral brain-derived neurotrophic factor (BDNF) levels in patients with depression [114–117]. Despite some limited evidence suggesting brain and peripheral concentrations of BDNF are associated in humans [118] and mice [119], BDNF concentrations in the brain cannot be inferred from BDNF levels in the blood [120]. Exercise increases BDNF expression in human skeletal muscle cells [121–123]. However, the brain contributes 70-80% of circulating BDNF during rest and exercise [122]. Therefore, exercise must directly increase BDNF levels in the brain. This increase could be explained through the following downstream signaling pathways [121]: 1) hepatic d-β-hydroxybutyrate (DBHB) inhibits histone deacetylases 2 and 3 (HDAC2/3) [124], 2) hepatic insulin-like growth factor-1 (IGF-1), 3) PGC1-α increases skeletal muscle expression of fibronectin type III domain-containing protein 5 (FNDC5) which in turn can release irsin [125–128], 4) lactate directly stimulates the production of irsin in the brain via the PGC1-α/FDNC5 pathway [129], 5) the myokine Cathepsin B (CTSB) [130], and 6) osteocalcin (OC) [107, 131–133]. These pathways might explain why acute exercise seems to protect against sleep deprivation-induced downregulation of BDNF in mice [134].

There is a complex interaction between sleep, depression, and BDNF levels [135, 136]. Diagnosis of depression [137, 138], symptom severity [139], and comorbid insomnia [140] are associated with lower serum BDNF levels in humans. Furthermore, low levels of BDNF are associated with less slow-wave sleep in humans [141]. Conversely, increasing brain BDNF enhances slow-wave activity in non-REM sleep in mice [142, 143].

Multiple mechanisms might explain the effect of BDNF on sleep. BDNF increases synaptic strength [144], which might increase slow-wave activity (SWA) in mice [145]. There is a positive feedback loop between BDNF and serotonin [146, 147]. Melatonin, in turn, is synthesized from serotonin in the pineal gland [148]. Melatonin, an essential circadian hormone, facilitates sleep and acts as a zeitgeber [149]. Exogenous melatonin has been used as an adjuvant treatment in major depressive disorder with mixed results [150]. Moreover, agomelatine, an antidepressant with melatonin agonist activity, results in comparable improvement of symptoms [151] and functioning [152] but is more tolerable compared to other antidepressants [151].

Hepatokines

Fibroblast growth factor 21 (FGF21) is a hormone produced by multiple cell types, including hepatocytes, adipocytes, and muscle fibers [101]. Acute exercise increases FGF21 expression in healthy humans, most likely via peroxisome proliferator-activated receptor alpha (PPARα) in hepatocytes but not muscle fibers [153]. FGF21 regulates circadian behavior via the suprachiasmatic nucleus [154] and lowers body temperature during the night in mice [155, 156]. Increased serum concentrations of IGF-1 are also associated with improved circadian rhythm sleep-wake disorder symptoms in school-aged children [157].

Kynurenine

Diagnosis of depression and severity of depressive symptoms is associated with the dysregulation of the kynurenine pathway of tryptophan degradation [158]. Tryptophan is converted to kynurenine (KYN) [159]. KYN can be converted to kynurenic acid (KYNA) by kynurenine aminotransferases (KAT) in astrocytes and the periphery [101]. While KYN can pass the blood-brain barrier, KYNA cannot [159]. KYNA in the brain decreases total sleep time, non-REM, and REM sleep duration in mice [160]. Hence, if KYN levels are reduced in the periphery, then less KYNA can accumulate in the brain.

There is mixed evidence concerning the acute effect of aerobic exercise on the kynurenine pathway in humans. While one study resulted in an increase of peripheral KYN [161], others showed a PGC1-α-dependent increase in peripheral KAT and KYNA [162, 163]. These discrepancies can be partially explained by the different exercise volumes (20 min vs. 150-km bicycle time trial) implemented in these trials. Regular mind-body and moderate and vigorous aerobic exercise over 12 weeks did not affect peripheral KYN or KYNA levels in patients with depression [164].

The mechanisms outlined above might also partially explain other effects of exercise that are relevant in the context of depression. Exercise-induced increases of IGF-1 and BDNF are also linked to synaptic and cognitive plasticity [165]. The antidepressant effect of exercise might be explained by lower kynurenine levels in the brain [162, 166]. Exercise-induced factors such as beta-hydroxybutyrate, irisin, and lactate also protect against ischemic stroke [167].

These putative tissue-brain crosstalk mechanisms of action are mainly based on animal data. Hence, it is uncertain whether these findings can readily be transferred to humans and especially patients with depression [168]. We are just beginning to elucidate the properties of the *human* blood-brain barrier [169]. Moreover, chronic sleep loss might disrupt the blood-brain barrier function [170]. Given its gatekeeper role, the blood-brain barrier is most likely central to understand the physiological mechanisms of exercise-induced effects on sleep in patients with depression. More research is needed to understand these potential physiological pathways.

8.3.2 Chronic effects on sleep

8.3.2.1 Mood, anxiety, and pain

Rates of comorbid chronic pain [171] and anxiety disorders [172] are high in patients with depression. Sleep is bidirectionally associated with chronic pain [173], anxiety, and depression [174]. Many meta-analyses have revealed the positive effect of aerobic, resistance, and mind-body exercises on depression [175–184]. Furthermore, regular aerobic, resistance, and mind-body (especially yoga) exercises positively affect anxiety [185–188]. Regular aerobic, resistance, and mind-body exercise also seem to improve pain [189]. Specifically, mind-body and motor control stabilization ameliorate back pain [190, 191]. This finding is relevant since comorbid depression and back pain are very frequent [192] and associated with higher societal costs [192, 193]. Exercise-induced improvements of pain, anxiety, and depression might partially mediate the effect on sleep.

8.3.2.2 Thermoregulation

Thermoregulation is an central factor of circadian and sleep regulation, which is impaired in depression and insomnia (see section 8.3.1.2). Thermoregulatory potency (as measured by distal-proximal skin temperature gradient) is an independent predictor of sleep-onset [64] and associated with slow-wave activity [80]. Aerobic [194], resistance [195], and mind-body [196] exercise improve thermoregulation (via distal skin vasodilation and sweating). Enhanced thermoregulation might, therefore, be another mechanism by which exercise improves sleep.

8.3.2.3 BDNF

Not all exercise types have a positive effect on resting BDNF levels. Dinoff et al. conducted a meta-analysis on the effects of regular aerobic exercise on BDNF levels in patients with depression [197]. Although there was a trend towards higher BDNF levels after an exercise intervention, the point estimate did not reach statistical evidence (SMD = 0.43, 95% CI: −0.06–0.92, p = 0.09). A more recent study also failed to find an effect of aerobic exercise on resting BDNF levels [198]. However, more research with sufficiently large sample sizes and adequate sampling techniques is needed. Of note, the acute increase of BDNF levels after aerobic exercise seems to remain constant over 16 weeks of training in patients with depression [198]. However, a meta-analysis in healthy individuals showed that the acute exercise-induced surge of peripheral BDNF levels is increased after regular aerobic training [199].

There is also a lack of studies investigating the effects of regular resistance exercise on BDNF in patients with depression [197]. In healthy individuals, resistance training did not increase resting levels of BDNF [200]. However, mind-body exercise increases resting BDNF in patients with depression [201, 202].

BDNF is associated with slow-wave activity, as noted in section 8.3.1.5. Hence, the potential increase of BDNF levels after regular training might explain the positive effect of exercise on sleep. Furthermore, Rethorst et al. [203] revealed that improvements in hypersomnia were associated with reductions of BDNF levels in patients with depression.

8.3.2.4 Arousal – HRV

Since arousal is considered a central etiopathogenic factor in insomnia (see section 1.4.3), improvements in HRV might partially mediate the effects of exercise on sleep. Regular aerobic [204] or mind-body [205] exercise improves HRV in patients with depression. Multiple meta-analyses mirror these findings in healthy individuals [206–209]. Moreover, exercise-induced weight loss also improves HRV [210]. Conversely, resistance exercise only seems to improve HRV measures in people with fibromyalgia or some type of somatic disorder, but not in healthy individuals [211]. Nevertheless, resistance exercise increases vagal output during submaximal aerobic exercise [212]. However, it should also be noted that some authors have attributed the increases in HRV after chronic exercise to changes in the sinus node, heart size, and heart rate rather than an increase in vagal activity [213].

8.4 Strengths and limitations

8.4.1 Systematic review and network meta-analysis

The main strength of the systematic review was the network meta-analytic synthesis that allowed to compare multiple interventions simultaneously. Network meta-analysis was ideal, considering the limited number of studies, the heterogeneous interventions, and the limited direct evidence (i.e., head-to-head comparisons of different exercise types). Thus, this method maximized the knowledge gain based on substantial statistical evidence.

An extensive search strategy, reviewed according to the PRESS guideline [214], was employed, and the search results were updated before publication. Multiple digital tools were used to increase the effectiveness and efficiency of the screening process in light of the large number of citations. The Systematic Review Accelerator was used for deduplication and keyword frequency analysis [215]. The results of the keyword frequency analysis were implemented in Covidence [216] and significantly accelerated the screening process. Covidence in combination with RevMan [217] were used to assess the risk of bias and generate the corresponding plots. Furthermore, the search strategy and results of the screening process were carefully documented.

The publication complied with the PRISMA-NMA guideline [218]. An established risk of bias tool was used. Exercise-specific tools to assess study quality (e.g., TESTEX [219]) were explicitly disregarded since they lack important aspects such as participant blinding. The clinical rationale for the definition of nodes was provided. Furthermore, the pooling of trials into nodes is transparently documented (incl. potential effect modifiers) and corroborates the transitivity assumption. The network meta-analysis was based on standardized mean differences at the end of the intervention (as opposed to the frequently used but problematic pre-post standardized mean differences) [220]. Lastly, multiple sensitivity analyses were conducted to analyze the robustness of the findings.

Despite these strengths, the systematic review also had some limitations. Any trials that included patients diagnosed with another significant physical disorder (e.g., cancer) were excluded. Although this may have limited external validity, it was a conscious decision to decrease indirectness and ensure that the transitivity assumption held. Although no trial had to be excluded due to the language, the literature search did find any trials reported in Chinese. Not including trials written in Chinese might partially explain why Jiang et al. [11] found larger effect sizes for mind-body exercise. The confidence in the findings was limited by the methodological quality of the trials included in the review. These limitations include 1) primarily small sample sizes, 2) not blinding outcome assessors, 3) not reporting methods to avoid selection or reporting bias, and 4) generally no follow-up, adverse, or secondary outcome data.

8.4.2 Randomized controlled trial

The randomized controlled trial was conducted and reported with methodological rigor. The measures to reduce the risk of bias constitute the main strength of the randomized controlled trial. Implementing a nondeterministic unweighted minimization algorithm (a restricted randomization technique) with evidence-based predictive factors ensured a random sequence generation. Multiple procedures ensured allocation concealment: 1) withholding all details of the minimization algorithm from study nurses (as recommended by SPIRIT guideline [221]), 2) allocating participants after baseline measurement, and 3) using a random element. Both the random sequence generation and the

allocation concealment reduced the risk of selection bias. Contamination through other physical activity in the control and intervention groups was quantified to assess the risk of performance bias. Outcome assessors were blinded against allocation (as well as time-point and each other's ratings) to diminish the risk of detection bias. Implementing intent-to-treat analysis and the state-of-the-art imputation technique [222] to replace missing values minimizes the risk of attrition bias. Reporting bias was eliminated by publishing the primary and secondary outcomes (publications 4 and 5). Lastly, the procedures listed above and other methodologically relevant factors were reported according to the CONSORT [223] and GRAPH [224] guidelines.

Outcomes were carefully selected to help inform patients, clinicians, researchers, and policy makers. Sleep efficiency was selected as the primary outcome for multiple reasons. It is not possible to blind patients (and study personnel) against allocation in exercise trials. Hence, using patient-reported outcomes would strongly increase the risk of detection bias. Patients with depression have been shown to have sleep initiation and sleep maintenance problems [87]. Sleep efficiency is the best single polysomnographic marker to capture both of these issues and early awakening. However, insomnia is defined by a deterioration of *subjective* sleep quality. Furthermore, non-restorative sleep is an important predictor of daytime impairment [225]. Hence, sleep quality of the previous night was also measured using a questionnaire recommended by the German guideline for Sleep Disorders [226]. Besides further polysomnographic outcomes, subjective pre-sleep arousal, cardiovascular autonomic modulation, daytime sleepiness, and adverse events were also assessed as secondary outcomes. These outcomes help to gain a more detailed understanding of potential effects and the benefit-to-harm ratio. The latter is especially relevant considering the caveat of exercise timing and the rationale thereof proposed by the current sleep hygiene recommendations [30].

Methodological rigor was also applied to statistical considerations. Sample size calculation was based on a detailed rationale. Nonetheless, the effect size found in publication 4 [2] was much smaller than the effects size discovered by Passos et al. [27]. The data of Passos et al. was used since it was the only trial that focused on patients with insomnia (no trial had been performed on patients with depression) and assessed sleep efficiency using polysomnography at the time [27]. Other studies lacked a non-exercise control group and focused on somewhat older patients [28] or analyzed the correlation between acute exercise and sleep over 16 weeks [26]. As mentioned above, outcomes were assessed using intention-to-treat analysis and missings values replaced by multiple imputation. Several sensitivity analyses were conducted (which all confirmed the primary analysis). Inter-rater agreement was analyzed using raw agreement in percent and Cohen's kappa since both variables have respective strengths and limitations [227]. Inter-rater reliability of the polysomnographic scoring was good (comparable to other studies [228, 229]).

The main strength of publication 5 [3] is the detailed analysis of nocturnal HRV. HRV measures were provided for pre-sleep, each sleep stage (although insufficient data for N1 precluded analysis), and the entire night. The analysis by sleep stage is especially relevant since REM and non-REM sleep are characterized by sympathetic and parasympathetic predominance, respectively [230]. Data collection, interbeat interval analysis, cleaning, and HRV calculation were performed following guidelines [224, 231]. The choice of HRV analysis parameters (e.g., Lomb-Scargle periodogram, averaging 5-minute segments, excluding segments where participants were upright) was based on careful methodological considerations, a review of the current literature, and an exchange with Prof. Julian Thayer (University of California, Irvine).

Some readers may question using a *submaximal* graded exercise test to determine the individual resistance for the intervention. Two lines of reasoning guided the decision for a submaximal graded exercise test. Firstly, there is a clinical rationale to limit the psycho-physiological strain of a graded exercise test for patients since they are often exhausted. Secondly, exercise prescription for patients with depression should not be based on intensities relative to maxima (VO_2max, maximal heart rate) but relative to individual anaerobic threshold and subjective exercise intensity [232, 233]. Performing a maximal graded exercise test might also increase the risk of premature test discontinuation by the patient [234]. The method to estimate the anaerobic threshold proposed by Dickhuth et al. [235] does not require maximal exertion. Therefore, the additional information generated by a maximal graded exercise test is of minimal utility. Choosing the appropriate initial load and increments is non-trivial and affects the validity of the estimated lactate threshold [236]. Hence, a formula that provided optimal initial load and increments was used based on age, sex, height, and distance in the six-minute walk test. Using this formula increased the standardization of the graded exercise test, thereby reducing interrater variability.

The limitations of the randomized controlled trial also need to be considered when interpreting the results. Inclusion and exclusion criteria were defined considering the trade-off between external and internal validity. While the inclusion of patients with psychiatric and somatic comorbidities increased the external validity, excluding patients who used hypnotic agents decreased it. Whether the findings of publications 4 and 5 can be transferred to patients who use hypnotics is unclear. The symptom severity of the patients included in this trial does not seem to differ from that of other patients treated in the psychosomatic in-patient ward of the OBERWAID clinic (based on the Hospital Anxiety and Depression Scale and Patient Health Questionnaire 9 data collected and published by the Swiss National Association for Quality Development in Hospitals and Clinics). However, it should be noted that hypnotics are widely prescribed, despite phase II and III trials evidently lacking external validity [237, 238].

A limited polysomnographic montage was used at baseline and follow-up. This montage included only one frontal EEG electrode making it significantly less cumbersome for patients compared to multi-channel EEG. Although this montage has been validated [239], it does not comply with the standards set forth by the American Academy of Sleep Medicine [240]. Moreover, it precluded more sophisticated analyses (e.g., quantitative EEG analysis). Despite the loss of information, this was a conscious tradeoff to increase the probability of successful patient recruitment. Patient recruitment is a crucial success factor of clinical trials. Approximately one in four clinical trials is discontinued, most frequently due to slow recruitment [241, 242]. A high burden for participants (e.g., uncomfortable measurements such as multichannel EEG) is a common reason for recruitment failure [243].

Multiple parameters of interest were not assessed to limit the burden on participants and lower the risk of dropouts. Although validated questionnaires are available (e.g., the SIMPAQ questionnaire [244]), baseline physical activity was not assessed. Quantifying baseline physical activity would have allowed for more secondary correlational analyses. Only the current symptom severity was assessed due to the short duration of the intervention. There was no attempt to quantify the frequency or duration of the current or past depressive episodes. Knowledge of previous depressive episodes might have helped to characterize the participants in more detail. Unlike pre-sleep arousal, the mood at bedtime was not assessed. Such an assessment would have enabled quantifying whether the exercise-induced improvements in mood persisted until bedtime. However, the changes in mood were not correlated with sleep outcomes (see appendix 9.1.3). Lastly, we disregarded nocturnal blood pressure

(measured continuously from pulse transit time) data. Although the algorithm was validated [245] according to guidelines [246], 10% of participants had physiologically unreasonably low values (i.e.., mean arterial pressure <60 mmHg).

The main limitation of publication 5 [3] was the lack of an a priori sample size calculation. A non-inferiority design would have been elegant, considering the time restraint and rationale put forth in the current sleep hygiene guideline [30]. Non-inferiority designs require a clinically meaningful non-inferiority margin to calculate the sample size [247]. Defining the non-inferiority margin based on the effect of antidepressants on HRV would fulfill the criteria above, considering the significance of HRV in depression and insomnia (see sections 1.4.2 and 1.4.3, respectively) and the frequency of antidepressant use. The meta-analysis of Alvares et al. [248] revealed that the effect of antidepressants on HRV in patients with a mood or anxiety disorder depends on the type of medication used. The effect sizes of tricyclic, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitor antidepressants on HRV were -0.45, -0.18, and 0.01 [248]. The resulting sample sizes would have been 168, 1’436, and 10’964 for tricyclic, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitor antidepressants respectively. Recruiting so many participants was considered unrealistic in the timeframe of the Ph.D. project. Moreover, though most feasible, the comparison with tricyclic antidepressants would have been of limited clinical utility. Selective serotonin reuptake inhibitor is the most frequently prescribed antidepressant, whereas tricyclic antidepressants are only prescribed in a minority of patients with depression (e.g., 13% in Switzerland [249] and 2% in the USA [250]). Lastly, testing for equivalence would have logically resulted in an even higher sample size (≥23’764). Therefore, it was decided to analyze the effect of exercise on nocturnal HRV using a superiority framework. This trail would provide initial data, which could later be aggregated with other trials in a meta-analysis.

8.5 Clinical implications

The findings of publications 2 have multiple implications for clinical practice. Compared to treatment as usual, regular vigorous strength training and mind-body exercise combined with treatment as usual can be recommended to improve sleep quality in patients with depression (low confidence). Compared to passive control, all exercise types and intensities can be recommended, except for moderate aerobic exercise to improve sleep quality (low to moderate confidence). These findings close significant knowledge gaps regarding the optimal type and intensity of exercise, as identified by the Swiss Society for Sports Psychiatry and Psychotherapy position paper on mental health and physical activity [251]. The choice of exercise type and intensity should be tailored to the individual's preferences and somatic comorbidities.

The results of publications 4 and 5 can inform practice recommendations. A single bout of moderate aerobic exercise lasting 30 minutes can be recommended to induce acute improvements of mood states in patients with depression. Moreover, a single bout of moderate-intensity aerobic exercise is likely not harmful to sleep or other symptoms.

8.5.1 The timing caveat of sleep hygiene guidelines

Current sleep hygiene recommendations do not recommend exercise after 02:00 pm, as exercise might release endorphins and hinder sleep onset [30]. This caveat on timing does not seem to be evidence-based. On the contrary, evidence from epidemiological [252] and intervention trials in healthy individuals [31] and patients with insomnia [25–29] show either no or a beneficial effect. Publications 4 and 5 confirm these findings. They were also the first publications to investigate the acute effect of exercise after 02:00 pm on sleep outcomes and pre-sleep and nocturnal arousal in patients with depression, to the best knowledge of the author. However, none of the studies mentioned above were equivalence or non-inferiority trials. Thus, the absence of evidence should not be mistaken as evidence of absence.

In clinical practice, multiple factors should be considered to decide whether exercise after 02:00 pm is reasonable. Since aerobic exercise in the evening might cause a phase delay in individuals with an early chronotype [95], these individuals should be encouraged to perform aerobic exercise in the morning but not in the evening. Considering the evidence base, it is highly questionable whether patients should entirely forgo exercise if it is not feasible before 02:00 pm. In these cases, an exercise titration approach seems sensible. Specifically, the duration and intensity of exercise can gradually be increased, and the duration between exercise and bedtime can gradually be decreased until optimum efficacy and feasibility are found. A sufficiently long recovery period between exercise cessation and bedtime should be maintained for core body temperature and HRV to return to baseline. The recovery period is crucial considering that thermoregulation [68–70] and autonomic cardiac control [253] are impaired in patients with depression but necessary for sleep onset [62–64, 254]. This duration will depend on the exercise variables (intensity, duration), the ambient temperature, and the thermoregulatory and cardiorespiratory capacity of the individual patient [255, 256]. Moreover, scheduling demands may vary during the week. On days where exercise is possible during the morning, aerobic or strength exercise can be scheduled. Mind-body exercises can be performed on those days that only allow for exercise in the evening.

8.5.2 Exercise as a polypill to improve somatic outcomes

The main advantage of exercise for patients with depression is the multitude of psychological and somatic benefits [257]. Numerous previous meta-analyses have established the positive effects of regular aerobic, resistance, and mind-body exercises on depression [175–184], anxiety [185–188], and pain [189–191]. Aerobic exercise can offset the increased risk for adverse somatic outcomes associated with depression and insomnia (see section 1.5.4). Multiple physiological pathways can explain this: improvement of inflammatory [258–260], oxidative [261], autonomic [204, 262], and hypothalamus-pituitary-axis [263] dysregulation, as well as cardiorespiratory fitness [264]. Publication 2 [1] extends the literature by adding evidence that mind-body exercise combined with treatment as usual and vigorous resistance exercise can improve sleep more compared to treatment as usual.

8.6 Future research

Publications 2, 4, and 5 have begun to close the research gaps identified in the introduction (see Figure 3). Further high-quality trials are needed to improve the confidence in the findings and reduce the uncertainty intervals. Furthermore, important questions outside the scope of this Ph.D. project remain unanswered. Scientific and societal relevance [265] should guide these future avenues of research. Designing and delivering exercise interventions to improve insomnia in patients with depression is an interdisciplinary endeavor. Nevertheless, future investigations can be viewed from different perspectives.

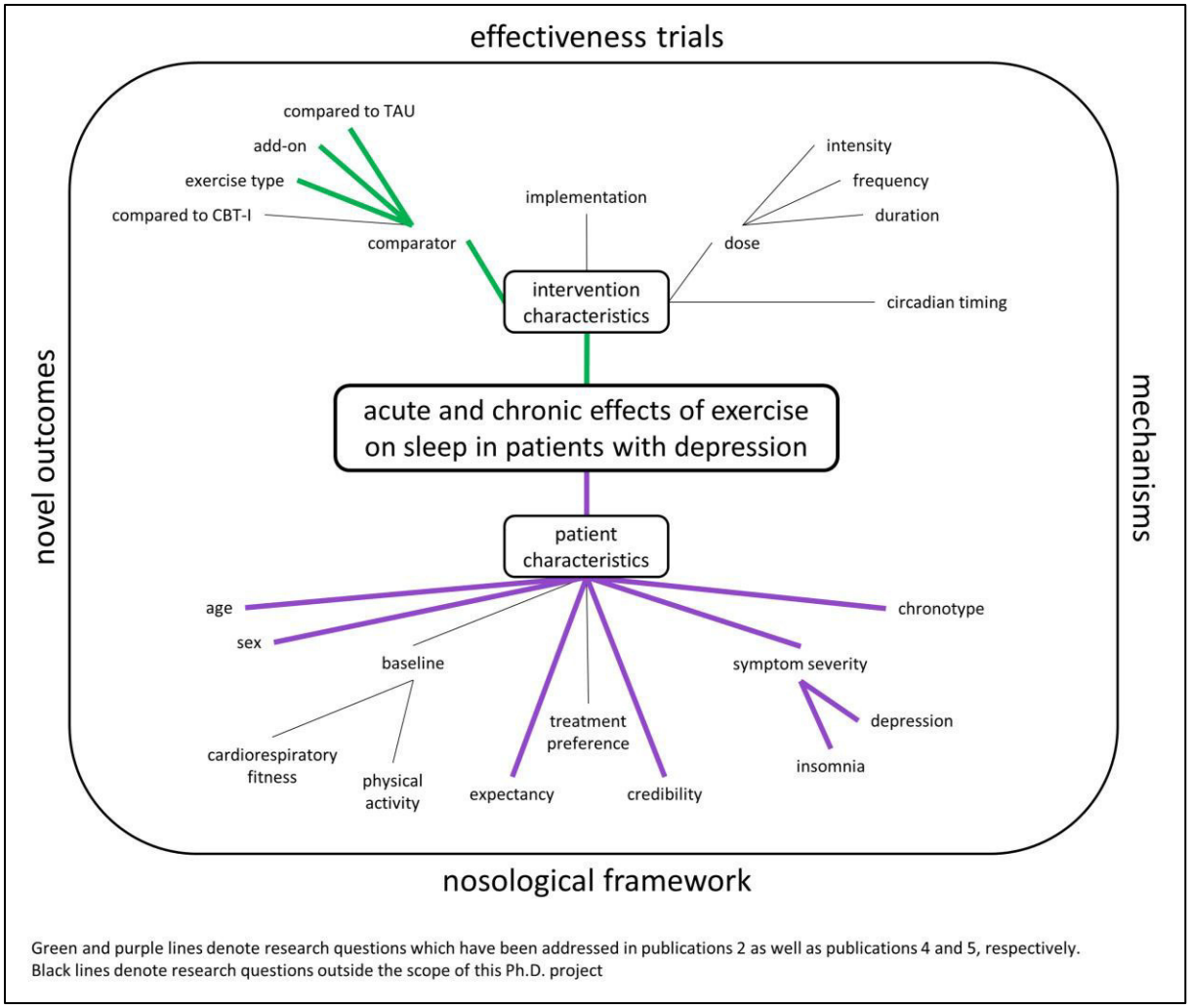

Figure 3: Research framework with partially answered and pending research questions

8.6.1 From the perspective of exercise science

Multiple lines of investigation are required to close knowledge gaps. Future trials should specifically investigate moderators. Quantifying the effect of potential moderators is essential to create an evidence base to prescribe exercise in a personalized manner [266].

Multiple intervention-related moderators should be investigated, considering previous findings and remaining knowledge gaps. The question of exercise intensity remains a stimulating topic, considering the findings of publication 2 [1]. Based on this data, investigating the effects of *vigorous* strength training seems to be one of the most promising lines of investigation to maximize efficiency. Moreover,

resistance exercise has been investigated less frequently compared to aerobic and mind-body exercise. Future trials should investigate the cumulative effect of vigorous strength training and treatment as usual to maximize utility for patient care. Preliminary evidence on high-intensity interval training is also encouraging because it may ameliorate depressive symptoms, improve cardiorespiratory fitness, and CV health more than moderate continuous exercise [267–269]. However, further high-quality evidence is needed to confirm these findings. Since adherence and dropout rates might be an issue in high-intensity interval training [270], innovative trials might specifically target these factors by varying delivery formats (e.g., groups) or exercise protocols (i.e., duration of intervals [271]). The prediction intervals of publication 2 (confer supplement 2, section 10) [1] can inform sample size calculations for studies aiming to compare different intensities or types of exercise. Lastly, future trials could aim to elucidate optimal aerobic and resistance training volume to ameliorate sleep in patients with depression, as was done for depressive symptoms [272].

Future trials could also investigate how the simultaneous application of interventions such as bright light therapy or cognitive training may potentially produce compounding effects. Depression is associated with circadian dysregulation [100]. Bright light, on the other hand, is the most potent zeitgeber [273]. Bright light is an accepted form of therapy [274] that improves symptoms of depression [275] and insomnia [276]. Hence, it would be very interesting to compare the effects of morning exercise with morning exercise augmented by simultaneous bright light exposure on circadian rhythm and sleep quality. Cognitive impairment occurs during a depressive episode [271, 272] and persists after remission [277]. Furthermore, cognitive dysfunction partially mediates functional impairment [278], which drives societal costs [279]. While mind-body exercises seem to improve cognition, aerobic and resistance exercise do not [280, 281]. These improvements might be attributed to the additional cognitive elements of mind-body exercises such as attentional awareness on breathing. Simultaneous exercise and cognitive tasks have been shown to have beneficial effects on cognition in older adults [282]. Considering these findings and the relevance of cognitive dysfunction in depression, this seems to be an up-and-coming line of research.

The moderating effect of participant characteristics also merits closer examination, based on previous findings [18, 283]. Besides age and gender, depression-related moderators (e.g., etiopathogenesis, symptom severity and constellation, duration of current episode, number of episodes) and sleep-related moderators (e.g., symptom severity and constellation) should be assessed in the context of exercise interventions. Potential moderators such as expectancy, credibility, adherence, baseline physical activity can be easily measured and should be assessed in all future exercise trials irrespective of study design. Despite their relevance to understanding placebo and nocebo effects, credibility and expectancy are rarely addressed in exercise trials [284, 285]. However, assessing these factors would increase internal validity since participants cannot be blinded and expectancy is an established effect modifier in depression [286, 287]. Baseline, follow-up, and changes of cardiorespiratory fitness should also be assessed but require more resources. Lastly, future trials should compare the effects of exercise in patients with and without hypnotic use.

Chronotype is another especially interesting patient-related moderator. Cross-sectional and interventional studies have revealed an interaction of chronotype and timing of exercise on sleep-related variables. These findings suggest that evening exercise induces a phase delay and reduces sleep quality in early chronotypes [95, 288, 289], while morning exercise induces a phase advance in early and late chronotypes [95, 290]. However, morning exercise might be a stressor for late chronotypes. Evening types have reported higher perceived exertion rates during morning exercise than morning

types [291]. Moreover, the interaction between chronotype and exercise timing also seems to affect the level of cortisol secretion in healthy individuals. Bonato et al. [292] showed that evening types had higher salivary cortisol secretions after morning exercise than morning types. However, cortisol secretion after evening exercise did not differ between chronotypes. Since participants were generally healthy in the trials mentioned above, these findings might not be transferable to patients with depression. Finding effective treatments to improve sleep for patients with evening chronotype is essential. Poor sleep quality mediates [293] the association between eveningness and depression severity [294]. Furthermore, evening chronotype predicts attenuated treatment response in patients with depression [295, 296]. Therefore, studying the interaction of chronotype and timing of exercise in patients with depression is a research priority.

8.6.2 From the perspective of sleep medicine

Polysomnographic recordings are comprised of multiple channels. Each of these channels contains a wealth of information, especially the EEG and ECG signals. The most common analysis method of polysomnographic data dissects these continuous signals into epochs (20 or 30 seconds) and assigns vigilance states (wake, N1, N2, N3, REM) according to specified rules (Rechtschaffen and Kales [297] or American Association of Sleep Medicine [240]).

Traditional analysis of polysomnographic data has multiple limitations [298]. Despite the digitization of recordings, the analysis of polysomnographies still relies on dissecting the continuous signal into discrete epochs (20 or 30 seconds). However, many physiological phenomena, such as the gradual nature of sleep stage shifts or brief episodes of wakefulness (<15 seconds), cannot be captured with such a low temporal resolution. The new sleep stage scoring rules set forth by the American Association of Sleep Medicine [240] have improved reliability slightly, resulting in a substantial overall inter-rater agreement of 80.6% (Cohen's kappa = 0.68) [228]. However, the distinction between non-REM sleep stages remains unreliable, even in highly trained and experienced scorers [299]. Moreover, manual sleep stage scoring is expensive due to the need for trained experts and the time-consuming nature of the task. Automated sleep scoring algorithms have been improved by recent advances in signal analysis, but their validity mostly remains unsatisfactory (with some notable exceptions, e.g. [300]). Furthermore, multiple barriers impede integration in clinical routine [301].

Discarding the previous paradigm of visual scoring of discrete epochs has spawned new analysis techniques and polysomnographic markers. Cardiopulmonary coupling is a spectrographic analysis based on the interaction of normal-to-normal sinus inter-beat intervals and electrocardiogram-derived respiratory dynamics [302]. Based on cardiopulmonary coupling, sleep stability is lower in patients with depression than healthy controls [303] but can be improved by cognitive behavioral therapy [304]. Cycling alternating pattern [305] is a periodic EEG pattern during non-REM sleep and is a marker of sleep instability [306]. Cycling alternating pattern analysis might detect differences in non-REM sleep between patients with depression and controls, which conventional sleep stage scoring might not [307]. The odds ratio product determines the probability of arousals or an awakenings in the next 30-seconds epoch [308]. This probability is calculated on 3-second epochs, providing a much higher temporal resolution than traditional scoring. Averaging the odds ratio product in the nine seconds after an arousal or an awakening (i.e., the ability to return to sleep after the arousal or awakening) has been proposed as a measure of sleep drive [309]. Envelope analysis provides a measure of neuronal synchrony [310]. Exercise has been shown to increase slow-wave stability using envelope analysis

[311]. Spectral analysis decomposes EEG data into frequency components expressed in relative or absolute power [18]. The clinical usefulness of such quantitative EEG analyses in the context of major depression is not yet fully understood [312]. However, the delta sleep ratio seems to be the most promising marker for future investigations. Lastly, automated topic modeling procedures [313] and high-density EEG recordings [314] have shown that patients with insomnia exhibit wake-like brain activity during non-REM sleep. In summary, the increased temporal resolution and sensitivity to change of these novel polysomnographic markers might uncover more subtle but potentially relevant effects of exercise interventions. To the best knowledge of the author, only very few trials have assessed the effects of exercise on sleep (regardless of the population studied) using these new markers (e.g., [315, 316]). Hence, future trials investigating exercise and collecting polysomnographic data should consider using these outcome variables.

Wearable technology, including wearable sleep and physical activity monitors, has been the number one fitness trend worldwide in previous years [317]. Hence, using wrist-worn and smartphone-based sleep trackers is a common phenomenon [318]. These devices are also increasingly implemented in research [319, 320], including large projects funded by the National Institutes of Health [321]. The major advantages of commercially available sleep trackers are their ease of use and low cost compared to polysomnography. This allows collecting and analyzing vast amounts of data on sleep and other behaviors such as exercise in subjects' natural surroundings (e.g., during the COVID-19 pandemic [322]). Despite these benefits, a central limitation of these commercial sleep trackers currently remains. Although the validity and accuracy of these devices are increasing [323], a substantial error at the level of the individual remains [324]. Considering the previous developments in data acquisition [325] and analysis [326], it is likely that commercial sleep trackers will capablebe able to measure sleep with high accuracy in the future. Once this is the case, it will be possible to investigate the bidirectional relationship between exercise and sleep in naturalistic settings using large data sets.

To conclude, future developments in signal acquisition and data processing are likely to enable a more fine-graned analysis of sleep with high temporal resolution. These types of analyses might provide new insights and are less likely to produce ceiling and floor effects compared to conventional epoch-based sleep scoring [327]. As these novel hardware and software technologies become disseminated to mass markets, wearable sleep and activity monitors will enable access to large high-quality datasets. Such data sets are likely to provide a more differentiated understanding of how exercise can affect sleep.

8.6.3 From the perspective of informing and improving patient care

Future trials should pay attention to specific aspects of study design, especially the choice of outcomes and comparators and overall methodological quality. Many trials (N=137) in publication 2 [1] had to be excluded from network meta-analysis because they did not report sleep outcomes. Considering the relevance of insomnia in depression (confer section 1.4.1), any trial investigating the effect of exercise in patients with depression should explicitly include patient-reported sleep outcomes [328]. The efficacy of exercise vs. passive control for depressive and insomnia symptoms is now well established. Trials should investigate how exercise compares against and augments guideline therapies (i.e., CBT-I and pharmacotherapy) to inform and improve future patient care. Previous systematic reviews [329–332] and publication 2 [1] have indicated that the risk of bias is high in many trials, and adverse effects are rarely reported. Hence, the research community should focus its resources on conducting trials

with methodological rigor, including the assessment of adverse effects. As in all areas of science, future trials should make their data accessible [333], ranging from the publication of data in repositories (e.g., for individual patient data meta-analyses) to large-scale collaborative initiatives of data collection [334].

From a societal perspective, effectiveness trials (i.e., trials assessing the performance of interventions in real-life settings) are important because they inform the transfer of research findings into practice. However, only one effectiveness trial on the effect of exercise in depression has been conducted so far [335], to the best knowledge of the author. Such effectiveness trials should investigate the scalability and cost-effectiveness of exercise as well as including sleep outcomes. Dropouts [336] and non-adherence [337] are common phenomena in patients with depression. Hence, trials that specifically aim to improve adherence to exercise interventions (e.g., through autonomous motivation strategies [338], feedback, monitoring [339], professional supervision [336], social interactions in group settings, music) are needed. A meta-analytic study revealed that physical activity levels decrease as treatment intensity decreases (i.e., from in-patient, to out-patient, to community treatment) [340]. While leisure-time physical activity is associated with less depression [341], sleep problems [342], and higher HRV [343], the opposite is true for occupational physical activity. Thus, interventions to increase leisure or transport physical activity, especially after inpatient treatment, should be tested in community settings (e.g., [344]).

Exercise could be a viable therapeutic approach to at least partially bridge the mental health care gap (i.e., the percentage of individuals who require treatment but do not receive it) [345]. The care gap for mental disorders is well documented and most pronounced in low- and middle-income countries [346, 347]. Those patients who do receive psychotherapy often have to wait multiple months [348]. During this period, symptoms deteriorate in some but not all patients [349, 350]. Exercise might be a viable treatment during and beyond this waiting period. A very recent randomized controlled trial provides initial evidence in favor of this hypothesis [351]. Further trials are needed to confirm this finding. Regular aerobic exercise can help close the physical morbidity and mortality gap [345, 352, 353] in depression (confer section 1.5.4). However, more high-quality randomized controlled trials are needed to confirm the effect of different exercise modes and intensities on somatic comorbidities and risk factors.

8.6.4 From the perspective of the nosological paradigm shift

Clinicians diagnose depression based on reports and observation of specific symptoms as defined in diagnostic manuals (e.g., ICD or DSM). These diagnostic manuals were derived deductively based on expert consensus [354]. These diagnostic frameworks distinguish some forms of depression (e.g., melancholic and atypical) [355]. Nevertheless, this nosological approach has been criticized as being non-specific [356, 357] because it cannot capture the heterogeneity of depressive symptomatology [358] and wide variations in treatment response [266]. Moreover, substantial cross-sectional [359] and longitudinal [360] overlap between atypical and melancholic depression within patients has been reported. This lack of specificity has driven the search for further phenotypic subtypes of depression. Approaches to identify subtypes are generally based on symptom patterns and biomarkers [356, 361]. However, these approaches have not led to the identification of consistent subtypes [361, 362]. One major limitation of the symptom-based approach is that similar symptom patterns can be caused by different etiopathogenetic mechanisms [361].

The transdiagnostic perspective, on the other hand, aims to understand processes that underlie seemingly distinct psychiatric disorders defined by DSM or ICD [363]. In this framework, processes are defined as descriptive (co-occurring) and mechanistic (causal or bidirectional) [364]. There is clear evidence that insomnia [363] and hyperarousal operationalized by HRV [365] are transdiagnostic markers of psychopathology.

Exercise is a transdiagnostic phenomenon of psychopathology. Lack of exercise [366] and low cardiorespiratory fitness [367] are predictors for mental health disorders. Exercise improves transdiagnostic targets of psychopathology (e.g., anxiety sensitivity, stress reactivity, general self-efficacy [368] and insomnia [369]) and disorder-specific symptoms of depression, anxiety [370], insomnia [371], attention deficit hyperactivity disorder [372], schizophrenia [373], and substance abuse disorders [374]. Lastly, exercise is a potent lifestyle factor to preserve and improve physical health in patients with psychopathologies [375]. However, the number of trials implementing exercise specifically as a transdiagnostic treatment remains very limited [40, 351, 376].

Future trials should, therefore, assess the usefulness of exercise as add-on therapy in populations with diverse mental health disorders. Specifically, these trials should assess the effects of exercise interventions on disease-specific and comorbid symptoms (including sleep and daytime functioning), mechanistic processes, and adverse events with long-term follow-ups. Despite the promise that the transdiagnostic approach holds, potential contraindications for certain patients need to be considered. These might include aerobic exercise training for patients with a very low body mass index (as this contributes to a negative energy balance) or high-intensity aerobic exercise for patients with bipolar disorder (especially during manic episodes [377]). Health practitioners should exercise caution when designing programs for these patients (e.g., resistance exercise aimed at hypertrophy for anorexia).

8.6.5 From a mechanistic perspective

Although publication 2 [1] demonstrates the efficiency of exercise to improve sleep in patients with depression, data on potential mechanisms of action is lacking. Potential mechanisms of action should be assessed multiple times throughout trials. Multiple assessments would allow elucidating the timing of mediators with respect to changes in outcomes.

Thermoregulation is perhaps one of the most promising potential mediators. Future trials could investigate how acute and chronic exercise interventions affect thermoregulation (i.e., distal-proximal skin gradient). This method necessitates highly accurate measurements. Telemetric pills might be an adequate method to assess core body temperature considering the limited accuracy of tympanic ear thermometers and low compliance with rectal measurements. Although telemetric pills are highly accurate at resting [378] and exercising [379] conditions, their high costs (price and time-consuming calibration) remain a challenge for widespread implementation in research.

More studies are needed to characterize acute and regular exercise effects on subjective arousal, nocturnal HRV, and BDNF levels. The pre-sleep arousal questionnaire [380] is a particularly useful tool due to its validity and brevity. Adequate intervention durations are critical when investigating the effects of regular exercise on HRV and BDNF. Improvements of resting HRV and BDNF-levels might occur with a delay, compared to improvements in mood or sleep. Assessing the effects of regular

exercise on *nocturnal* HRV seems a particularly auspicious method, given the results in healthy individuals [381, 382].

Multiple signaling pathways might mediate the effect of exercise on sleep, as discussed in section 8.3. Hence, future studies could analyze these potential mediators in blood samples with respect to changes in sleep outcomes. Such analysis would be especially interesting for tryptophan in the context of high-intensity exercise. Sharp drops in tryptophan levels have been observed after high-intensity exercise [161]. Tryptophan is a precursor for hormones such as melatonin and serotonin (with chrono-regulating effects) but also for KYN (with adverse effects on sleep in mice), see section 8.3.1.5. Therefore, changes in circulating tryptophan levels after high-intensity exercise might be an interesting marker, primarily when exercise is performed very close to bedtime and might disrupt sleep [31]. Although academically highly interesting, the cost-benefit ratio of muscle biopsies to measure factors within the skeletal muscle cells (e.g., *Bmal1*) might be somewhat disproportionate in patients with depression.

There has been a development from evidence-based medicine to personalized medicine in recent years [383]. Pharmacogenomic testing, i.e., selecting antidepressant medication based on genetic variants that influence the pharmacokinetics and pharmacodynamics, has been shown to improve outcomes in patients with depression [384–386]. There is also substantial evidence that genetic variants alter the affective response to exercise [387]. Future trials might consider the effects of exercise on the epigenome [388] and the microbiome [389] in the context of depression [390, 391]. Of note, there is evidence that genetics may not predict cardiorespiratory adaptations to an exercise intervention [392–395]. In summary, investigating the interaction between genetics and exercise is very complex but a highly interesting endeavor.

8.7 Conclusion

This Ph.D. project had two overarching goals: 1) to consolidate the existing evidence of regular exercise on sleep and 2) to extend the knowledge concerning the acute effects of exercise on sleep and nocturnal arousal in patients with depression. The systematic review and network meta-analysis compared regular aerobic, resistance, and mind-body exercises with different intensities. The clinical trial quantified the effect that 30 minutes of moderate-intensity aerobic exercise has on subjective and objective measures of sleep, daytime sleepiness, mood, adverse effects, as well as pre-sleep and nocturnal arousal. Multiple conclusions can be drawn from the publications within this Ph.D. thesis.

The systematic review and network meta-analysis extend the current knowledge with regards to two questions: 1) which exercise types and intensities are most conducive to improve sleep and 2) how do exercise interventions compare to treatment as usual on sleep in patients with depression. All investigated exercise types and intensities– except moderate aerobic exercise – improve sleep quality more than passive control. Moderate aerobic exercise might not be inefficient per se, but the somewhat smaller point estimate and large confidence interval preclude statistical significance. Vigorous strength exercise is significantly more efficacious than all other types and intensities of exercise. Only vigorous resistance exercise and mind-body exercise combined with treatment as usual are more efficacious than treatment as usual. This was the first publication to meta-analytically aggregate trials investigating the effects of regular exercise on sleep in patients with depression. The network meta-analytic approach produced emergent findings, which could not have been derived through other methods.

The randomized controlled trial produced findings that should be considered in the context of sleep hygiene recommendations. No evidence for a negative effect on objectively or subjectively measured sleep quality nor daytime sleepiness was found. Furthermore, there was no evidence to suggest that exercise altered pre-sleep or nocturnal arousal. These results are contrary to the hypothesis outlined in sleep hygiene recommendations. However, a single bout of moderate-intensity aerobic exercise had a strong and consistently positive effect on mood. Lastly, a non-significant trend towards lower somatic symptom severity immediately post-exercise was noted.

In summary, this Ph.D. thesis has addressed knowledge gaps regarding the optimal type and intensity of regular exercise and the effect of a single bout of aerobic exercise on sleep. Thereby, this thesis has strengthened the level of evidence supporting the use of regular and acute exercise to improve sleep and mood, respectively, in patients with depression. Remission of insomnia symptoms is central to achieving an optimal long-term depression trajectory. These findings can help clinicians, patients, and policymakers to take informed action, thus improving the treatment of depression and ultimately coping with the growing disease burden of depression.

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9 Appendix

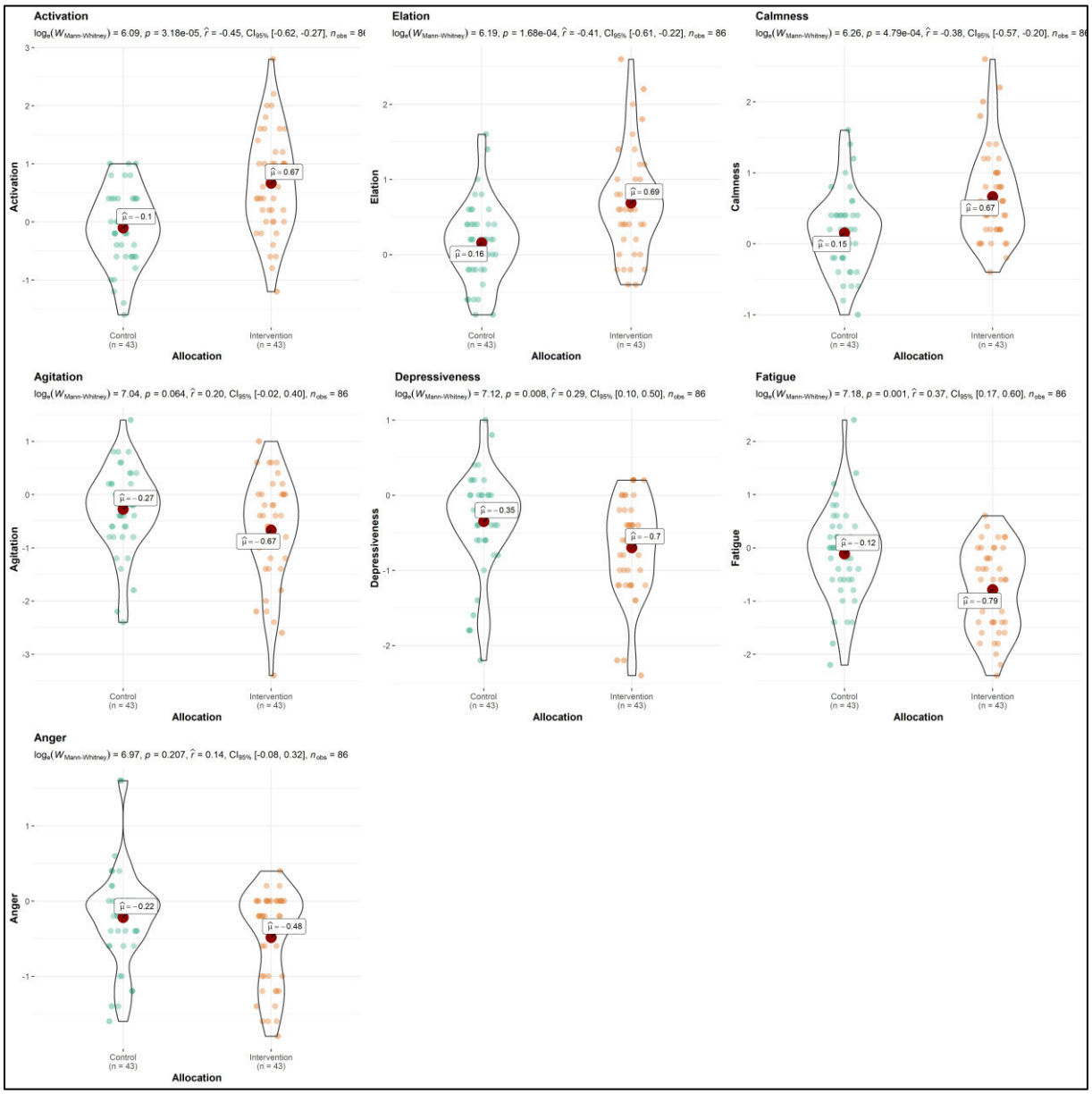
9.1 Additional analyses

9.1.1 Patients who reported having hypersomnia

Item 3 of the PHQ-9 questionnaire asks whether the patient had trouble falling or staying asleep or slept too much. We added a follow-up question asking which one of these symptoms (trouble falling or staying asleep vs. sleeping too much) was more relevant. Of the 92 patients included in the randomized control trial, 20 (28%) reported sleeping too much.

None of the results of publication 4 [2] changed, when excluding patients who reported sleeping too much. For example, the point estimate of allocation on sleep efficiency in the ANCOVA model remained similar and non-significant in patients who had trouble falling and staying asleep (β = -0.83, 95% CI = -4.66 to 3.00, *p* = 0.67) and those patients who slept too much (β = -1.04, 95% CI = -6.13 to 4.05, *p* = 0.66) when compared to the primary analysis (β = -0.93, 95% CI = -4.32 to 2.47, *p* = 0.59).

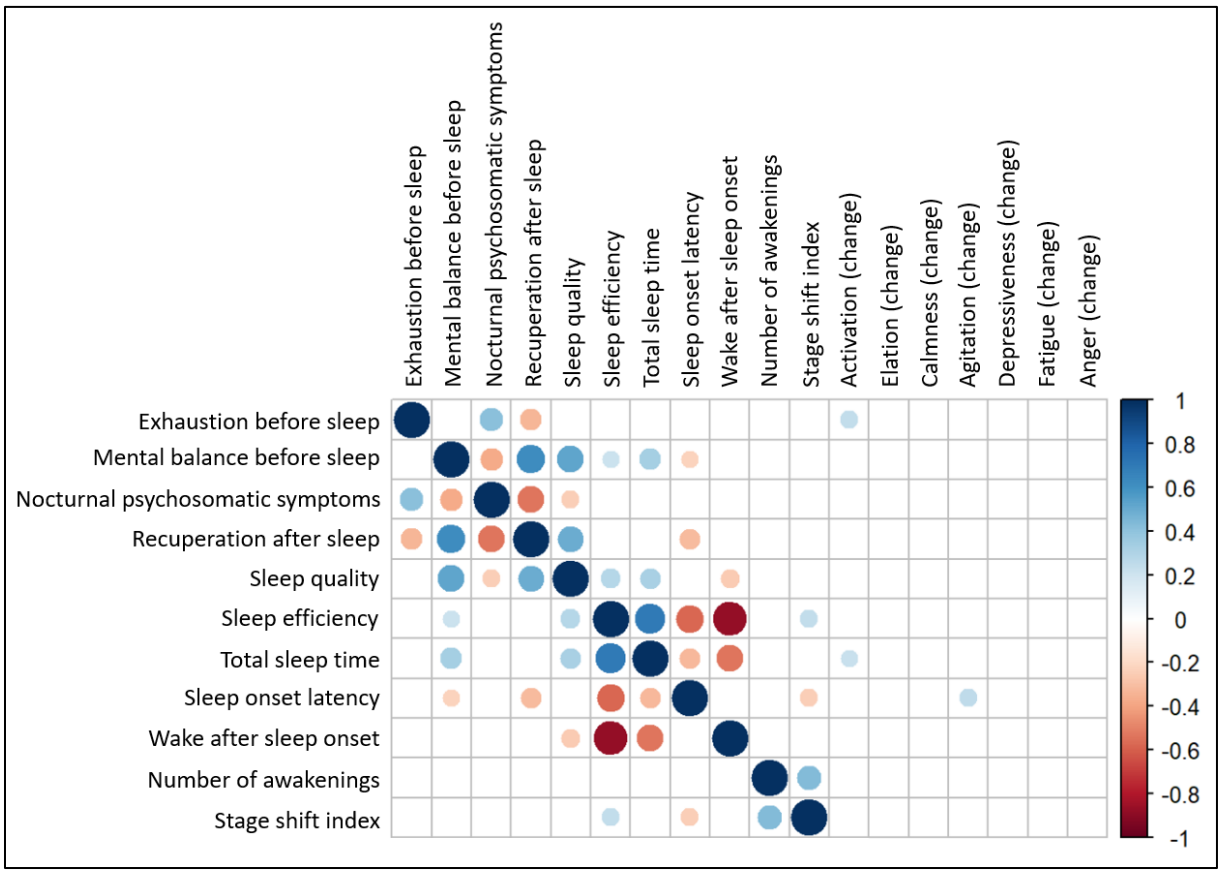
9.1.2 Absolute changes of mood from pre- to post-intervention by allocation



Likert scale: *1* = not at all to *5* = very much

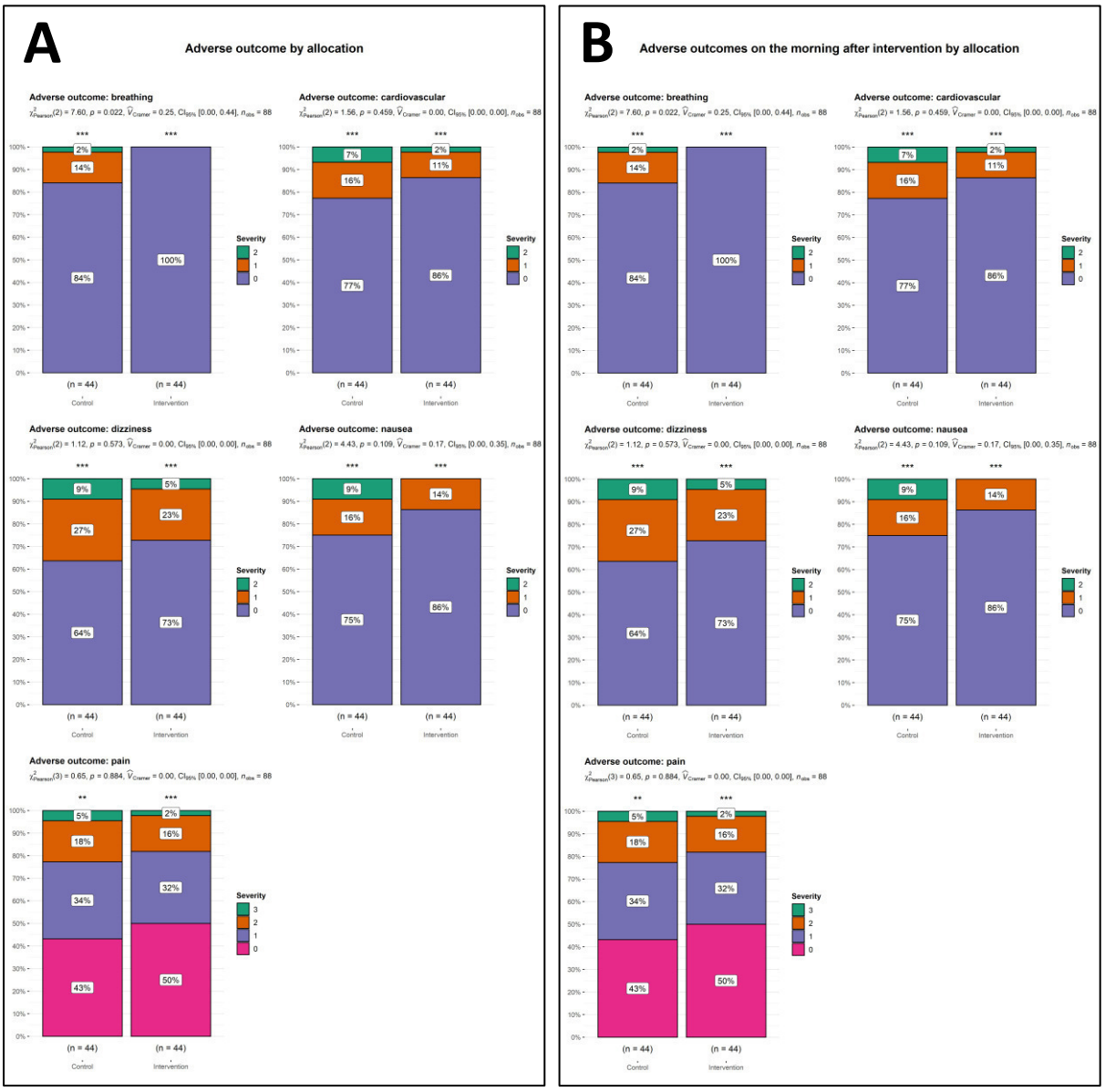
Please note: the subscale contemplativeness had insufficient internal consistency (Cronbach's alpha: 0.47 and 0.64 for pre- and post-intervention, respectively) and was not further analyzed

9.1.3 Heatmap of Spearman's rank correlation coefficients of mood changes (from pre- to post-exercise) with sleep outcomes in night 2



Circle sizes and color saturation denote the magnitude of correlations, with blue indicating positive and red indicating negative correlation coefficients. The absence of circles denotes non-significant correlation coefficients.

9.1.4 Adverse events immediately post-exercise (A) and after awakening on day 5 (B)



Likert scale: *0* = not at all to *4* = very much